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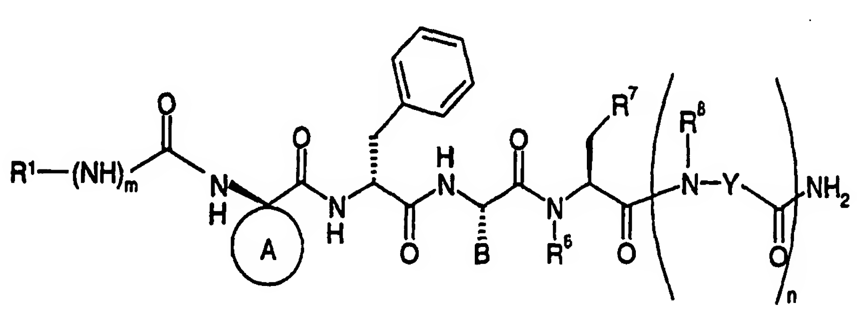
(54) Title: SELECTIVE LINEAR PEPTIDES WITH MELANOCORTIN-4 RECEPTOR (MC4-R) AGONIST ACTIVITY



(S1)

(57) Abstract: The present invention relates to peptides comprising the structure (S1) wherein R^1, R^6, R^7, R^8, m, n, A and B are as defined in the description and claims. Such compounds selectively activate melanocortin-4 (MC-4) receptor activity.

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SELECTIVE LINEAR PEPTIDES WITH MELANOCORTIN-4 RECEPTOR (MC4-R) AGONIST ACTIVITY

Background of the Invention

Obesity is widely recognized as a serious health problem for the developed countries, and has reached epidemic status in the United States. More than 50% of the U.S. population is considered overweight, with >25% diagnosed as clinically obese and at considerable risk for heart disease, non-insulin dependent diabetes mellitus (NIDDM), hypertension, and certain cancers. This epidemic presents a significant burden on the health care system as projected obesity treatment costs of more than $70 billion annually are expected in the U.S. alone. Strategies for treating obesity include reducing food intake or enhancing the expenditure of energy.

It has been demonstrated that, when injected into the third ventricle of the brain or intraperitoneally, a cyclic heptapeptide analog of α-melanocyte stimulating hormone (αMSH) having melanocortin-4 receptor (MC4-R) agonist activity caused long lasting inhibition of food intake in mice. This effect was reversible when co-administered with a MC4-R antagonist. (Fan, et al., Nature (1997) 385: 165-168) Therefore, agonists of MC4-R activity would be useful in treating or preventing obesity.

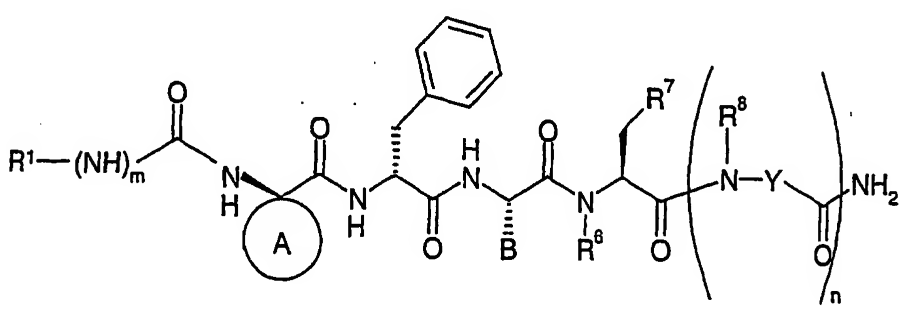
There are five known melanocortin receptors based on sequence homology that ranges from 35-60% homology between family members (Cone, et al., Rec. Prog. Hormone Res. (1996) 51: 287-318), but these receptors differ in their functions. For example, the MC1-R is a G-protein coupled receptor that regulates pigmentation in response to the αMSH, which is a potent agonist of MC1-R. (Cone, et al., *ibid.*). Agonism of the MC1-R receptor results in stimulation of the melanocytes which causes eumelanin and increases the risk for cancer of the skin. Agonism of MC1-R can also have neurological effects. Stimulation of MC2-R activity can result in carcinoma of adrenal tissue. The effects of agonism of the MC3-R and MC5-R are not yet known. All of the melanocortin receptors respond to the peptide hormone

class of melanocyte stimulating hormones (MSH). These peptides are derived from pro-opiomelanocortin (POMC), a prohormone of 131 amino acids that is processed into three classes of hormones; the melanocortins (α, β and γ), adrenocorticotropin hormone (ACTH), and various endorphins (e.g. lipotropin) (Cone, et al., *ibid.*). Because of their different functions, simultaneous agonism of the activities of multiple melanocortin receptors has the potential of causing unwanted side effects. Therefore it is desirable that an agonist of MC4-R be more selective for the MC4-R than for one or more of the other melanocortin receptors.

Haskell-Luevano, et al. (Peptides (1996) 17(6): 995-1002) disclose peptides that contain the tripeptide (D)Phe-Arg-Trp and exhibit melanotropic (skin darkening) activity in the frog *(Rana pipiens)* skin bioassay. Haskell-Luevano, et al. *(ibid.)* do not disclose any compound of formula I, II or III described below.

Summary of the Invention

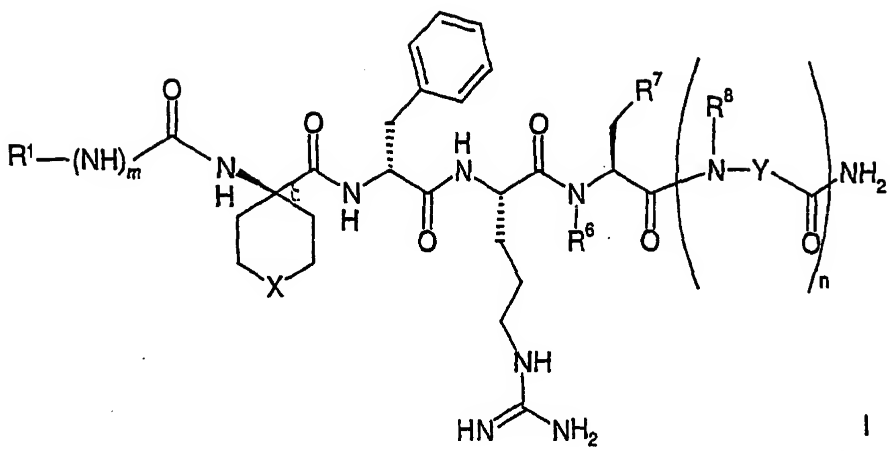
This invention relates to compounds comprising the following structure (S1):



(S1)

wherein R^1, R^6, R^7, R^8, m, n, A and B are as defined in a) to d) and wherein the compound is selected from the group consisting of

a) a compound of the formula:



I

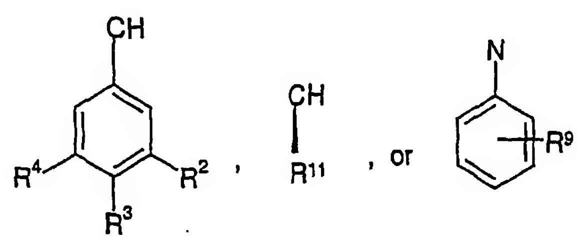
wherein

m is 0 or 1;

n is 0 or 1;

R^1 is an unsubstituted linear or branched alkyl having from 1 to 8 carbon atoms; linear or branched alkyl having from 1 to 8 carbon atoms mono-substituted by phenyl or carboxyl; unsubstituted phenyl; or phenyl mono-substituted by fluoro, chloro or linear or branched alkyl having from 1 to 4 carbon atoms;

X is



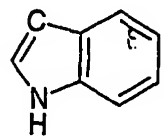
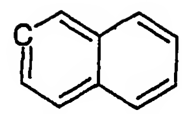
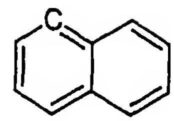
wherein R^2, R^3 and R^4 are independently hydrogen or a linear or branched alkoxy having from 1 to 4 carbon atoms, wherein when R^3 is alkoxy, R^2 and R^4 are both hydrogen;

R^9 is hydrogen, linear or branched alkyl having from 1 to 3 carbons, linear or branched alkoxy having from 1 to 3 carbons, or unsubstituted phenoxy;

R^{11} is cyclohexyl, cycloheptyl, or a branched alkyl having from 3 to 8 carbon atoms;

R^6 is hydrogen or methyl;

R^7 is

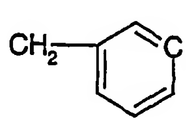
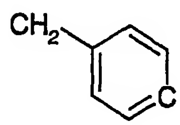
,  or 

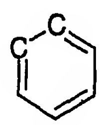
Y is

$$-CH_2-,\ -CH_2CH_2-,\ \text{or}\ -\overset{|}{C}H-CH_3,$$

and R^8 is hydrogen or methyl; or

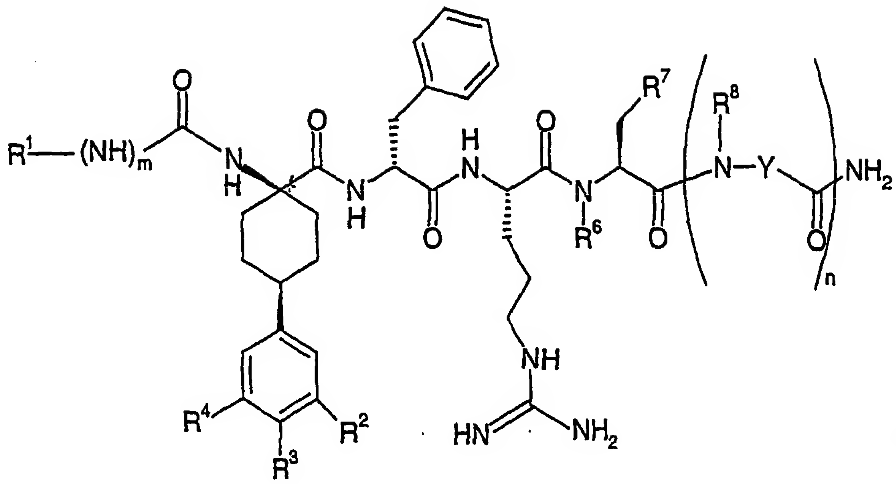
Y is

, , or



and R^8 is hydrogen;

b) a compound of the formula:



IA

wherein

m *is 0* or *1;*

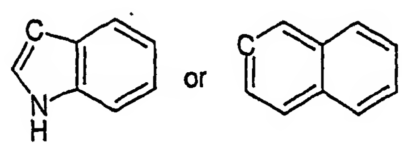
n is 0 or 1;

R^1 is an unsubstituted linear or branched alkyl having from 1 to 8 carbon atoms; linear or branched alkyl having from 1 to 8 carbon atoms mono-substituted by phenyl or carboxyl; unsubstituted phenyl; or phenyl mono-substituted by fluoro, chloro or linear or branched alkyl having from 1 to 4 carbon atoms;

R^2, R^3 and R^4 are independently hydrogen; a linear or branched alkyl having from 1 to 4 carbon atoms; hydroxy, a linear or branched alkoxy having from 1 to 4 carbon atoms; or chloro, wherein when R^3 is alkyl, hydroxy, alkoxy or chloro, R^2 and R^4 are both hydrogen;

R^6 is hydrogen or methyl;

R^7 is

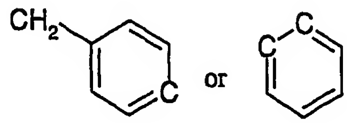


Y is

$$-CH_2-,\ -CH_2CH_2-,\ \text{or}\ -\overset{|}{C}H-CH_3,$$

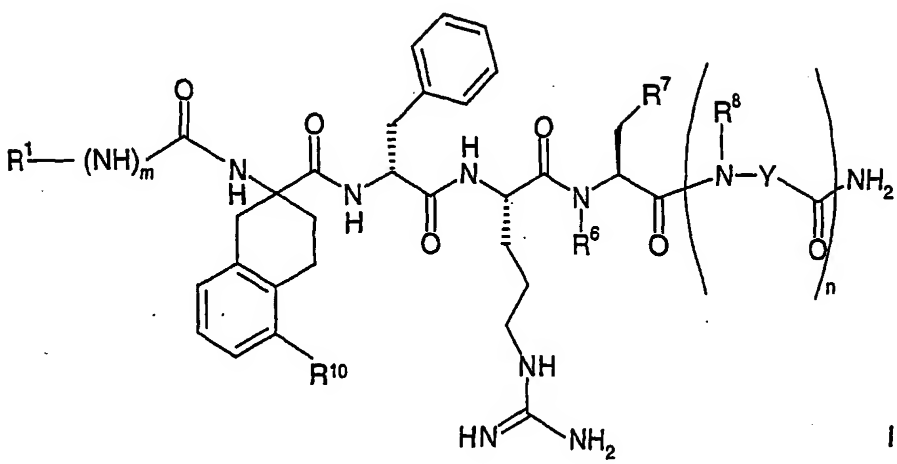
and R^8 is hydrogen or methyl; or

Y is



and R^8 is hydrogen;

c) a compound of the formula:



II

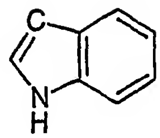
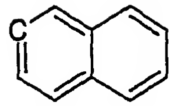
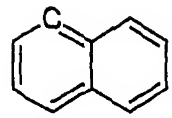
wherein

m is 0 or 1;

n is 0 or 1;

R^1 is an unsubstituted linear or branched alkyl having from 4 to 8 carbon atoms; linear or branched alkyl having from 1 to 8 carbon atoms mono-substituted by phenyl or carboxyl; or unsubstituted phenyl; or phenyl mono-substituted by fluoro, chloro or linear or branched alkyl having from 1 to 4 carbon atoms;

R^7 is

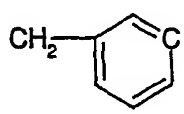
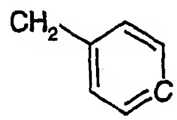
 ,  or 

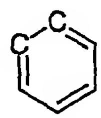
Y is

$-CH_2-$, $-CH_2CH_2-$, or $-\overset{|}{C}H-CH_3$,

and R^8 is hydrogen or methyl; or

Y is

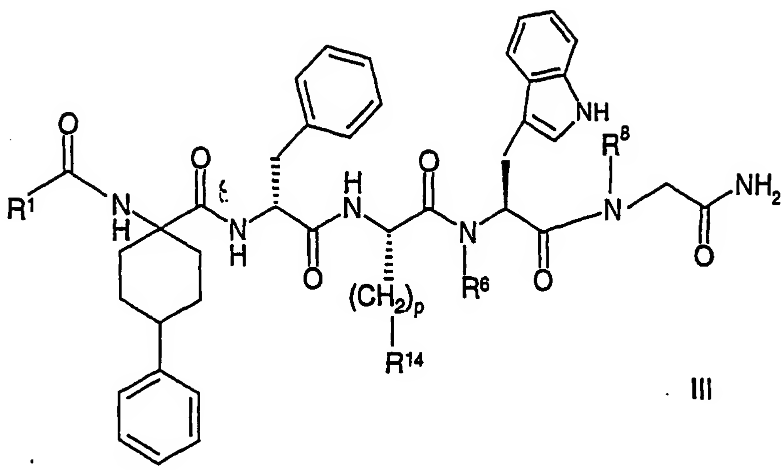
 ,  , or



and R^8 is hydrogen;

R^{10} is hydrogen, halo, linear or branched alkyl having from 1 to 3 carbon atoms, linear or branched alkoxy having from 1 to 3 carbon atoms, or $-NR^{12}R^{13}$ wherein R^{12} and R^{13} are each independently a linear or branched alkyl having from 1 to 3 carbons or together are $-(CH_2)_q-$ wherein q is 3, 4 or 5; and

d) a compound of the formula:



III

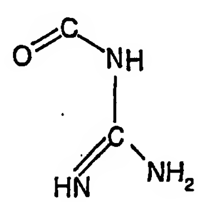
wherein

R^1 is unsubstituted linear or branched alkyl having from 4 to 8 carbon atoms;

R^6 is hydrogen or methyl;

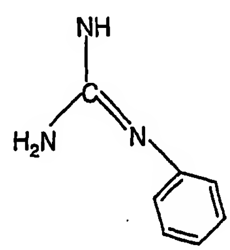
R^8 is hydrogen or methyl;

p is 2, 3 or 4 and R^{14} is



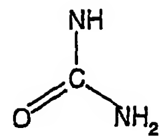
,

or p is 4 and R^{14} is

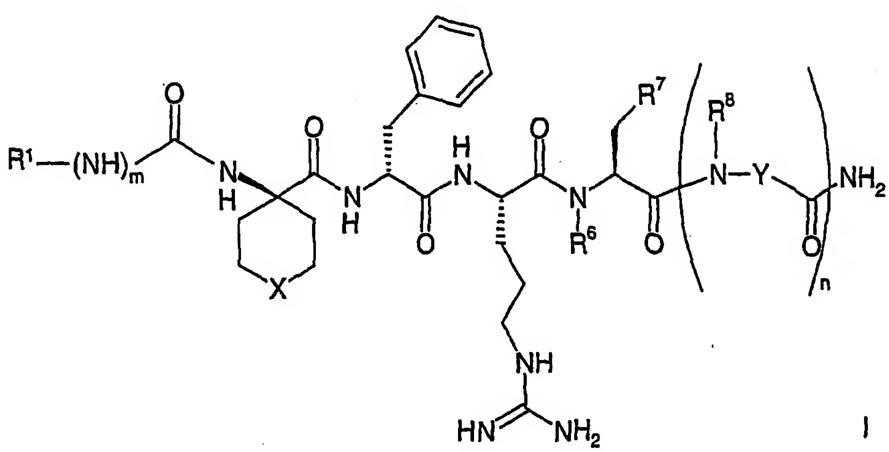


,

or p is 3 and R^{14} is

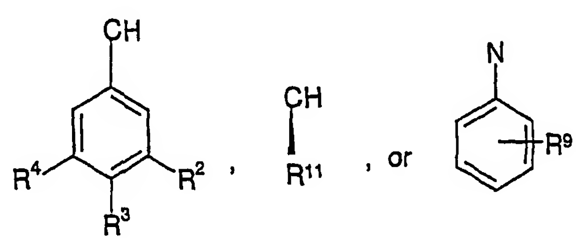


This invention provides a compound of the formula:

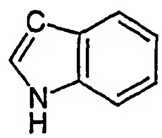


I

In compounds of formula I m is 0 or 1. n is 0 or 1. R^1 is an unsubstituted linear or branched alkyl having from 1 to 8 carbon atoms; linear or branched alkyl having from 1 to 8 carbon atoms mono-substituted by phenyl or carboxyl; unsubstituted phenyl; or phenyl mono-substituted by fluoro, chloro or linear or branched alkyl having from 1 to 4 carbon atoms. X is



R^2, R^3 and R^4 are independently hydrogen or a linear or branched alkoxy having from 1 to 4 carbon atoms, wherein when R^3 is alkoxy, R^2 and R^4 are both hydrogen. R^9 is hydrogen, linear or branched alkyl having from 1 to 3 carbons, linear or branched alkoxy having from 1 to 3 carbons, or unsubstituted phenoxy. R^{11} is cyclohexyl, cycloheptyl, or a branched alkyl having from 3 to 8 carbon atoms. R^6 is hydrogen or methyl. R^7 is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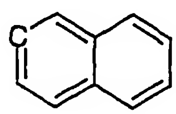
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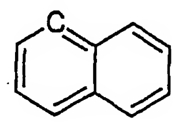
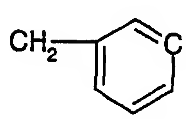


Y is

$$-CH_2-,\ -CH_2CH_2-,\ \text{or}\ -\overset{|}{C}H-CH_3,$$

and R^8 is hydrogen or methyl; or
Y is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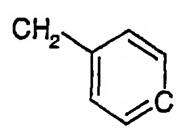
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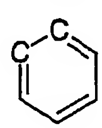
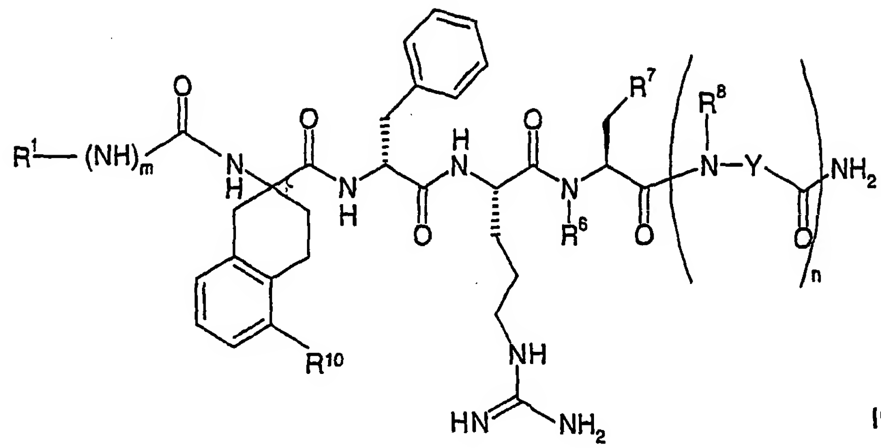


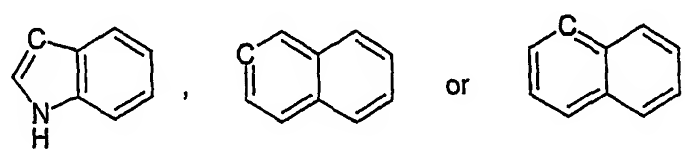
and R^8 is hydrogen.

This invention provides a compound of the formula:



II

In the compounds of formula II m is 0 or 1. n is 0 or 1. R^1 is an unsubstituted linear or branched alkyl having from 4 to 8 carbon atoms; linear or branched alkyl having from 1 to 8 carbon atoms mono-substituted by phenyl or carboxyl; or unsubstituted phenyl; or phenyl mono-substituted by fluoro, chloro or linear or branched alkyl having from 1 to 4 carbon atoms. R^7 is

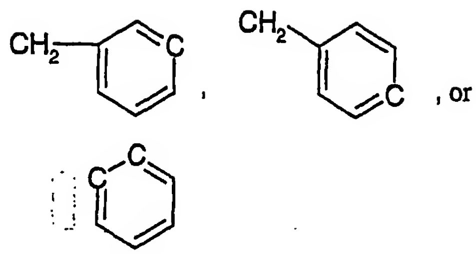


Y is

$$-CH_2-,\ -CH_2CH_2-,\ \text{or}\ -\overset{|}{C}H-CH_3,$$

and R^8 is hydrogen or methyl; or

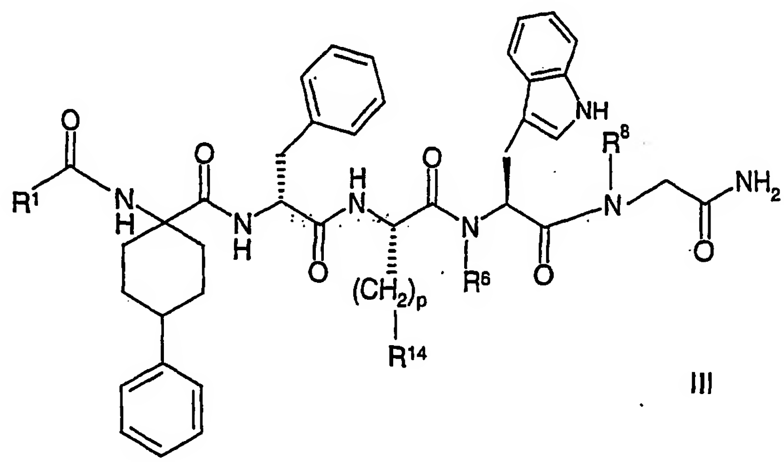
Y is



and R^8 is hydrogen.

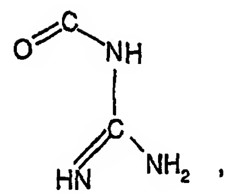
R^{10} is hydrogen, halo, linear or branched alkyl having from 1 to 3 carbon atoms, linear or branched alkoxy having from 1 to 3 carbon atoms, or $-NR^{12}R^{13}$ wherein R^{12} and R^{13} are each independently a linear or branched alkyl having from 1 to 3 carbons or together are $-(CH_2)_q-$ wherein q is 3, 4 or 5.

This invention provides a compound of the formula:

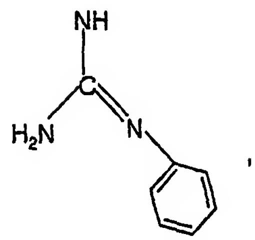


III

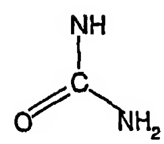
In the compounds of formula III, R^1 is unsubstituted linear or branched alkyl having from 4 to 8 carbon atoms. R^6 is hydrogen or methyl. R^8 is hydrogen or methyl. p is 2, 3 or 4 and R^{14} is



or p is 4 and R^{14} is



or p is 3 and R^{14} is



The compounds of formulae I, II and III as well as Penta-Adpc-(D)Phe-Arg-Trp-Gly-NH_2 and Penta-Ape-(D)Phe-Arg-Trp-Gly-NH_2 are agonists of the MC4-R. It is known that agonists of MC4-R activity cause reduction of food intake in a mouse model of human obesity. Therefore the compounds of formula I are useful in the treatment or prevention of obesity.

All of the compounds of formulae I, II and III exemplified below as well as Penta-Adpc-(D)Phe-Arg-Trp-Gly-NH_2 and Penta-Ape-(D)Phe-Arg-Trp-Gly-NH_2 were tested for MC4-R agonist activity and MC1-R agonist activity in the *in vitro* assay described below in Biological Activity Example A. All of the tested compounds had an EC50 for MC4-R agonist activity of less than 500 nM, and all exhibited at least 10-fold greater MC4-R agonist activity than MC1-R agonist activity. In contrast, the compound Bu-His-(D)Phe-Arg-Trp-

Gly-NH_2 (Example 30) exhibited greater MC1-R agonist activity than MC4-R agonist activity.

Detailed Description of the Invention

Nomenclature and Abbreviations

The nomenclature used to define the peptides is that typically used in the art wherein the amino group at the N-terminus appears to the left and the carboxyl group at the C-terminus appears to the right. By natural amino acids is meant one of the naturally occurring amino acids found in proteins, i.e., Gly, Ala, Val, Leu, Ile, Ser, Thr, Lys, Arg, Asp, Asn, Glu, Gln, Cys, Met, Phe, Tyr, Pro, Trp, and His. Where the amino acid has isomeric forms, it is the L form of the amino acid that is represented unless otherwise explicitly indicated.

The following abbreviations or symbols are used to represent amino acids, protecting groups, solvents, reagents and the like.

Symbol	Meaning
β-Ala	beta-Alanine
(2)-Nal	(2)-Naphthylalanine
Atc	2-Aminotetraline-2-carboxylic acid
5-BrAtc	5-Bromo-2-aminotetraline-2-carboxylic acid
5-ClAtc	5-Chloro-2-aminotetraline-2-carboxylic acid
5-MeOAtc	5-Methoxy-2-aminotetraline-2-carboxylic acid
5-EtOAtc	5-Ethoxy-2-aminotetraline-2-carboxylic acid
5-iPrOAtc	5-Isopropoxy-2-aminotetraline-2-carboxylic acid
5-MeAtc	5-Methyl-2-aminotetraline-2-carboxylic acid
5-EtAtc	5-Ethyl-2-aminotetraline-2-carboxylic acid
5-iPrAtc	5-Isopropyl-2-aminotetraline-2-carboxylic acid
5-DmaAtc	5-Dimethylamino-2-aminotetraline-2-carboxylic acid
Sar	Sarcosine (N-methylglycine)

Cit	Citrulline
Apc	1-Amino-4-phenylcyclohexane-1-carboxylic acid
4-HOApc	1-Amino-4-(4-hydroxyphenyl)cyclohexane-1-carboxylic acid
4-MeOApc	1-Amino-4-(4-methoxyphenyl)cyclohexane-1-carboxylic acid
3-MeOApc	1-Amino-4-(4-methoxyphenyl)cyclohexane-1-carboxylic acid
4-EtOApc	1-Amino-4-(4-ethoxyphenyl)cyclohexane-1-carboxylic acid
4-iPrOApc	1-Amino-4-(4-isopropoxyphenyl)cyclohexane-1-carboxylic acid
4-MeApc	1-Amino-4-(4-methylphenyl)cyclohexane-1-carboxylic acid
4-ClApc	1-Amino-4-(4-chlorophenyl)cyclohexane-1-carboxylic acid
Appc	4-Amino-1-phenylpiperidine-4-carboxylic acid
2-MeAppc	4-Amino-1-(2-methylphenyl)piperidine-4-carboxylic acid
2-iProAppc	4-Amino-1-(2-isopropoxyphenyl)piperidine-4-carboxylic acid
3-MeAppc	4-Amino-1-(3-methylphenyl)piperidine-4-carboxylic acid
3-MeOAppc	4-Amino-1-(3-methoxyphenyl)piperidine-4-carboxylic acid
4-MeAppc	4-Amino-1-(4-methylphenyl)piperidine-4-carboxylic acid
4-ClAppc	4-Amino-1-(4-chlorophenyl)piperidine-4-carboxylic acid
4-PhOAppc	4-Amino-1-(4-phenoxyphenyl)piperidine-4-carboxylic acid
Achc	1-Amino-4-cyclohexylcyclohexane-1-carboxylic acid
Adpc	1-Amino-4-diphenylcyclohexane-1-carboxylic acid
Ape	1-Amino-4-phenylcyclohex-3-ene-1-carboxylic acid
Abc	1-Amino-4-*tert*-butylcyclohexane-1-carboxylic acid
3-Amb	3-Aminomethyl benzoic acid
4-Amb	4-Aminomethyl benzoic acid
2-Aba	2-Aminobenzoic acid
Bu	Butyl
Penta	Pentyl
Fmoc	9-Fluorenylmethoxycarbonyl
Pmc	2,2,5,7,8-Pentamethylchroman-6-sulfonyl
CH_2Cl_2	Methylene chloride
CH_3CN	Acetonitrile
DMF	Dimethylformamide

DIPEA	N, N-Diisopropylethylamine
TFA	Trifluoroacetic acid
HOBT	N-Hydroxybenzotriazole
DIC	N, N'-Diisopropylcarbodiimide
BOP	Benzotriazol-1-yloxy-tris-(dimethylamino)phosphonium Hexafluorophosphate
PyBroP	Bromo-tris-pyrrolidino-phosphonium hexafluorophosphate
HBTU	2-(1H-Benzotriazol-1-yl)-1,1,3,3-tetramethyluronium Hexafluorophosphate
FAB-MS	Fast atom bombardment mass spectrometry
ES-MS	Electrospray mass spectrometry
NBSC	2-Nitrobenzenesulfonyl chloride
DEAD	N,N-diethylazodicarboxylate
Ph	Phenyl

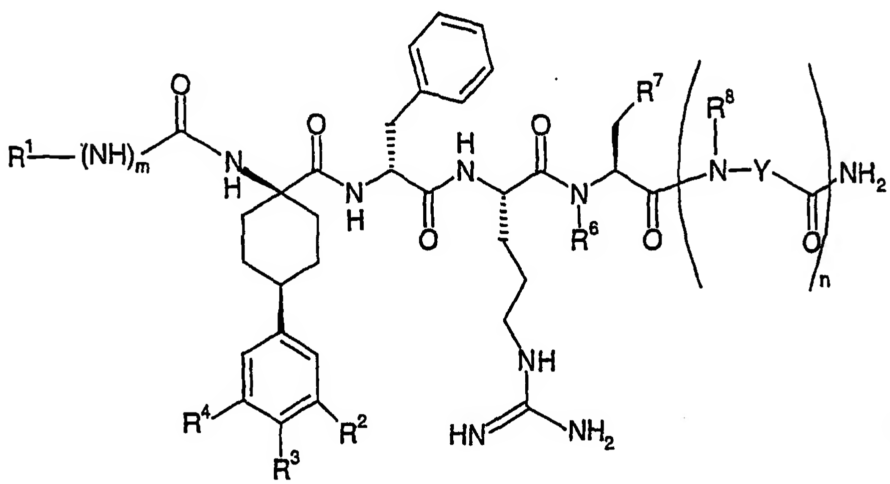
Setting forth the substituted amino acid, in parentheses indicates analogs of the peptide sequence. Derivatization of the N-terminal amino group, is indicated to the left of the N-terminal substitution, separated by a hyphen. That is, for example, Ac-His-(D)Phe-Arg-Trp-Gly-NH_2 indicates a peptide having an amino acid sequence in which an acetyl group has been substituted for hydrogen at the N-terminus. The suffixes "-OH" and "-NH_2" following the hyphen or the parentheses refer to the free acid and amide forms of the polypeptide, respectively.

The term "alkyl", unless otherwise defined, relates to saturated hydrocarbons with 1 to 8 carbon atoms. Alkyl groups can be linear, such as e.g. methly, ethyl, n-propyl, n-butyl or n-penteyl, or they can also be branched such as e.g. i-propyl or t-butyl. The term "lower", e.g. in "lower alkyl" relates to groups that have 1 to 6 carbon atoms.

Detailed Description of Compounds

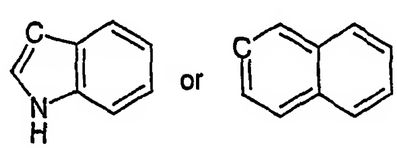
In compounds of formula I, it is generally preferred that R^6 and R^8 are both hydrogen, n is 1 and R^7 *is either the first or the second of the substructures shown above. Also preferred are* compounds of formulae IA, IB or IC as shown below.

Compounds of formula IA, are represented as follows:

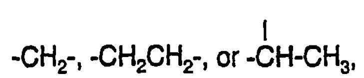


IA

In the compound of formula IA, m is 0 or 1. n is 0 or 1. R^1 is an unsubstituted linear or branched alkyl having from 1 to 8 carbon atoms; linear or branched alkyl having from 1 to 8 carbon atoms mono-substituted by phenyl or carboxyl; unsubstituted phenyl; or phenyl mono-substituted by fluoro, chloro or linear or branched alkyl having from 1 to 4 carbon atoms. R^2, R^3 and R^4 are independently hydrogen; a linear or branched alkyl having from 1 to 4 carbon atoms; hydroxy, a linear or branched alkoxy having from 1 to 4 carbon atoms; or chloro, wherein when R^3 is alkyl, hydroxy, alkoxy or chloro, R^2 and R^4 are both hydrogen. R^6 is hydrogen or methyl. R^7 is

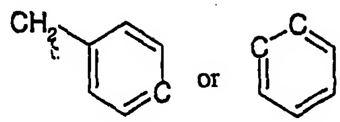


Y is



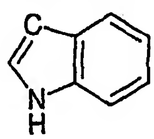
and R^8 is hydrogen or methyl; or

Y is



R^8 is hydrogen.

In the compounds of formula IA, R^7 can be either a tryptophan side chain or a 1- or 2-naphthyl group. In compounds of formula IA in which R^7 is a tryptophan side chain, i.e.

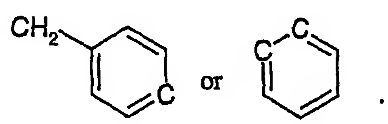


n can be either 0 or 1. Examples of such compounds in which n is 0 include Penta-Apc-(D)Phe-Arg-Trp-NH_2 and Penta-Apc-(D)Phe-Arg-N-methylTrp-NH_2. In compounds of formula IA in which R^7 is a tryptophan side chain and n is 1, Y can be a linear or branched alkyl group selected from methylene, ethylene or methyl-substituted methylene, i.e.

$$-CH_2-,\ CH_2CH_2-,\ \text{or}\ \ \begin{array}{c} | \\ -CH-CH_3 \end{array}$$

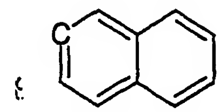
or one of the aryl-containing moieties shown above. In compounds of formula IA in which R^7 is a tryptophan side chain and n is 1, Y is methylene, ethylene or methyl-substituted methylene, m can be 0 or 1. Examples of such compounds in which m is 1 include Bu-Carbamoyl-Apc-(D)Phe-Arg-Trp-Gly-NH_2, Bu-carbamoyl-Apc-(D)Phe-Arg-Trp-Ala-NH_2, and Bu-Carbamoyl-Apc-(D)Phe-Arg-Trp-β-Ala-NH_2. In compounds of formula IA in which R^7 is a tryptophan side chain, n is 1, Y is methylene, ethylene or methyl-substituted methylene and m is 0, the phenyl ring of the Apc group can be either unsubstituted (i.e. R^2, R^3 and R^4 are hydrogen) or substituted. In such compounds in which the phenyl ring of the Apc group is unsubstituted, R^1 can be, for example, an unsubstituted linear alkyl such as in

the compounds Penta-Apc-(D)Phe-Arg-Trp-Gly-NH_2, Penta-Apc-(D)Phe-Arg-Trp-Sar-NH_2, Penta-Apc-(D)Phe-Arg-N-methylTrp-Gly-NH_2, Bu-Apc-(D)Phe-Arg-Trp-Ala-NH_2, or Bu-Apc-(D)Phe-Arg-Trp-β-Ala-NH_2; or unsubstituted phenyl such as in the compounds Phenylacetyl-Apc-(D)Phe-Arg-Trp-Gly-NH_2, Phenylacetyl-Apc-(D)Phe-Arg-Trp-Ala-NH_2, or Phenylacetyl-Apc-(D)Phe-Arg-Trp-Ala-NH_2. In such compounds in which the phenyl ring of the Apc group is substituted, one preferred substitution pattern is wherein R^3 is alkyl, hydroxy, alkoxy or chloro (more preferably R^3 is hydroxy or alkoxy) and R^2 and R^4 are hydrogen. Examples include Penta-4-ClApc-(D)Phe-Arg-Trp-Gly-NH_2, Penta-4-MeApc-(D)Phe-Arg-Trp-Gly-NH_2, Penta-4-HOApc-(D)Phe-Arg-Trp-Gly-NH_2, Penta-4-MeOApc-(D)Phe-Arg-Trp-Gly-NH_2, Penta-4-EtOApc-(D)Phe-Arg-Trp-Gly-NH_2, and Penta-4-iPrOApc-(D)Phe-Arg-Trp-Gly-NH_2. Another preferred substitution pattern is wherein R^2 is alkoxy, R^3 is hydrogen and R^4 is hydrogen, for example in the compound Penta-3-MeOApc-(D)Phe-Arg-Trp-Gly-NH_2. In compounds of formula IA in which R^7 is a tryptophan side chain and n is 1, and Y is

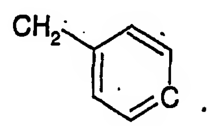


m can be 0 or 1. Examples of such compounds in which m is 1 include Bu-carbamoyl-Apc-(D)Phe-Arg-Trp-2-Aba-NH_2 and Bu-carbamoyl-Apc-(D)Phe-Arg-Trp-3-Amb-NH_2. Examples of such compounds in which m is 0 include Bu-Apc-(D)Phe-Arg-Trp-2-Aba-NH_2, Phenylacetyl-Apc-(D)Phe-Arg-Trp-2-Aba-NH_2, Bu-Apc-(D)Phe-Arg-Trp-3-Amb-NH_2, Phenylacetyl-Apc-(D)Phe-Arg-Trp-3-Amb-NH_2, Bu-Apc-(D)Phe-Arg-Trp-4-Amb-NH_2, and Phenylacetyl-Apc-(D)Phe-Arg-Trp-4-Amb-NH_2.

In compounds of formula IA in which R^7 is 2-naphthyl, i.e.

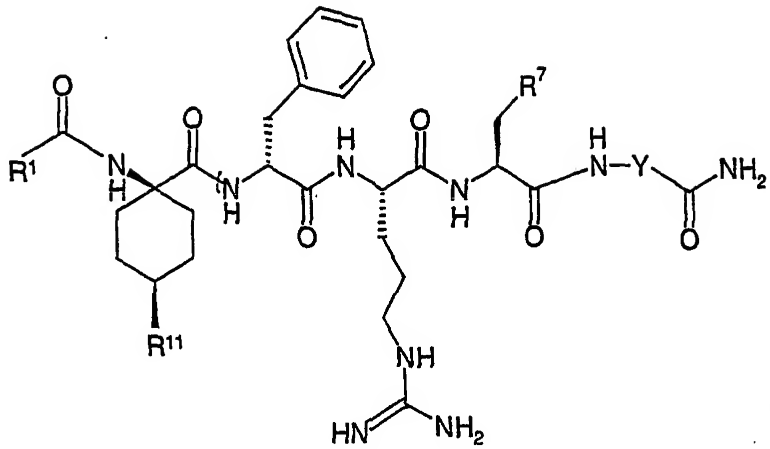


it is preferred that R^2, R^3 and R^4 are hydrogen. Examples of such compounds include Penta-Apc-(D)Phe-Arg-N-methyl(2)Nal-NH_2 and Bu-Carbamoyl-Apc-(D)Phe-Arg-(2)Nal-Gly-NH_2. In compounds of formula IA in which R^7 is 2-naphthyl, it is preferred that n is 1 and m is 0. In compounds of formula IA in which R^7 is 2-naphthyl, n is 1 and m is 0, and Y is methylene, ethylene or methyl-substituted methylene, R^1 can be, for example an unsubstituted linear alkyl. Examples of such compounds include, Penta-Apc-(D)Phe-Arg-(2)Nal-Gly-NH_2, Bu-Apc-(D)Phe-Arg-(2)Nal-Gly-NH_2, Ac-Apc-(D)Phe-Arg-(2)Nal-Gly-NH_2, Penta-Apc-(D)Phe-Arg-N-methyl (2)Nal-Gly-NH_2, Bu-Apc-(D)Phe-Arg-(2)Nal-Ala-NH_2, and Bu-Apc-(D)Phe-Arg-(2)Nal-beta-Ala-NH_2. Alternatively R^1 can be, for example, unsubstituted phenyl, or alkyl substituted by phenyl or carboxyl. Examples of such compounds include Benzoyl-Apc-(D)Phe-Arg-(2)Nal-Gly-NH_2, 3-carboxylpropanoyl-Apc-(D)Phe-Arg-(2)Nal-Gly-NH_2, and 3-carboxylpropanoyl-Apc-(D)Phe-Arg-(2)Nal-Gly-NH_2. In compounds of formula IA in which R^7 is 2-naphthyl, n is 1 and m is 0, and Y is



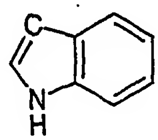
It is preferred that R^1 is unsubstituted lower alkyl. Examples of such compounds include Bu-Apc-(D)Phe-Arg-(2)Nal-3-Amb-NH_2, Bu-Apc-(D)Phe-Arg-(2)Nal-2-Aba-NH_2, and Bu-Apc-(D)Phe-Arg-(2)Nal-4-Amb-NH_2.

Compounds of formula IB are represented as follows:



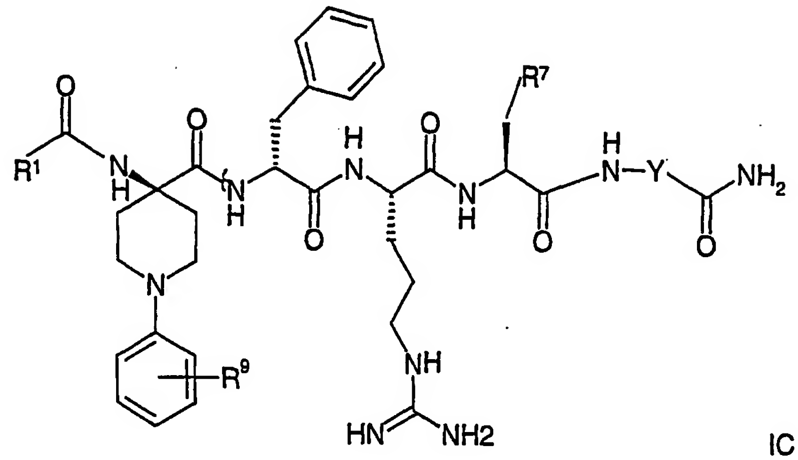
IB

In the compound of formula IB, R^1 is an unsubstituted linear or branched alkyl having from 1 to 8 carbon atoms. R^7 is



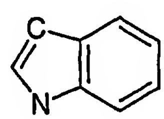
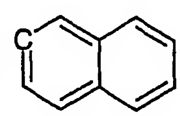
R^{11} is cyclohexyl, or a branched alkyl having from 3 to 8 carbon atoms. Y is methylene, i.e. -CH_2-. Examples of compounds of formula IB include Penta-Abc-(D)Phe-Arg-Trp-Gly-NH_2 and Penta-Achc-(D)Phe-Arg-Trp-Gly-NH_2.

Compounds of formula IC are represented as follows:



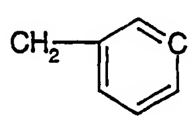
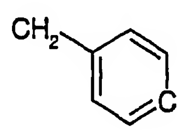
IC

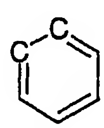
In the compound of formula IC, R^1 is an unsubstituted linear or branched alkyl having from 1 to 8 carbon atoms. R^7 is

 or  ;

Y is

$$\text{-}CH_2\text{-},\ \text{-}CH_2CH_2\text{-},\ \text{-}\overset{|}{C}H\text{-}CH_3,$$

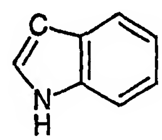
 ,  , or

 ; and

R^9 is hydrogen, a linear or branched alkyl having from 1 to 3 carbon atoms, a linear or branched alkoxy having from 1 to 3 carbon atoms, fluoro, chloro, or unsubstituted phenoxy.

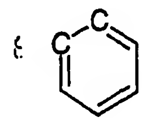
Examples of compounds of formula IC in which R^9 is hydrogen include Penta-Appc-(D)Phe-Arg-Trp-Gly-NH_2 and Penta-Appc-(D)Phe-Arg-(2)Nal-Gly-NH_2. Examples of compounds of formula IC in which R^9 is a linear or branched alkyl having from 1 to 3 carbon atoms include Penta-2-MeAppc-(D)Phe-Arg-Trp-Gly-NH_2, Penta-2-iPrAppc-(D)Phe-Arg-Trp-Gly-NH_2, Penta-3-MeAppc-(D)Phe-Arg-Trp-Gly-NH_2 and Penta-4-MeAppc-(D)Phe-Arg-Trp-Gly-NH_2. Examples of compounds of formula IC in which R^9 is a linear or branched alkoxy having from 1 to 3 carbon atoms or unsubstituted phenoxy include Penta-3-MeOAppc-(D)Phe-Arg-Trp-Gly-NH_2 and Penta-4-PhOAppc-(D)Phe-Arg-Trp-Gly-NH_2. Examples of compounds of formula IC in which R^9 is chloro include Penta-4-ClAppc-(D)Phe-Arg-Trp-Gly-NH_2.

In the compound of formula II it is generally preferred that R^6 and R^8 are hydrogen. R^7 can be, for example a tryptophan side chain, i.e.



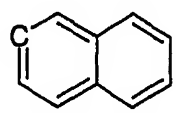
or 2-naphthyl. When R^7 is a tryptophan side chain it is generally preferred that n is 1. Among the compounds of formula II in which R^6 and R^8 are hydrogen; R^7 is a tryptophan side chain, and n is 1, are included compounds in which Y is -CH_2- and m is 0. Examples of such compounds in which R^{10} is hydrogen or a linear or branched alkyl having from 1 to 3 carbon atoms are included Bu-Atc-(D)Phe-Arg-Trp-Gly-NH_2, Penta-5-Me-(D,L)Atc-(D)Phe-Arg-Trp-Gly -NH_2, Penta-5-Et-(D,L)Atc-(D)Phe-Arg-Trp-Gly -NH_2 and Penta-5-iPr-(D,L)Atc-(D)Phe-Arg-Trp-Gly-NH_2. Examples of such compounds in which R^{10} is halo include Penta-5-Br-(D,L)Atc-(D)Phe-Arg-Trp-Gly-NH_2, Penta-5-Br-Atc-(D)Phe-Arg-Trp-Gly-NH_2 and Penta-5-Cl-(D,L)Atc-(D)Phe-Arg-Trp-Gly-NH_2. Examples of such compounds in which R^{10} is linear or branched alkoxy having from 1 to 3 carbon atoms include Penta-5-MeO-(D,L)Atc-(D)Phe-Arg-Trp-Gly -NH_2, Penta-5-EtO-(D,L)Atc-(D)Phe-Arg-Trp-Gly -NH_2 and Penta-5-iPrO-(D,L)Atc-(D)Phe-Arg-Trp-Gly-NH_2. Examples of such compounds in which R^{10} is -$NR^{12}R^{13}$ wherein R^{12} and R^{13} are each methyl include Penta-5-DmaAtc-(D)Phe-Arg-Trp-Gly-NH_2.

Among the compounds of formula II in which R^6 and R^8 are hydrogen; R^7 is a tryptophan side chain, and n is 1, are included compounds in which Y is



and R^{10} is halo. Examples of such compounds include Bu-(D,L)5-BrAtc-(D)Phe-Arg-Trp-2-Aba-NH_2, Bu-carbamoyl-(D,L)-5-BrAtc-(D)Phe-Arg-Trp-2-Aba-NH_2 and Phenylacetyl-(D,L)-5-BrAtc-(D)Phe-Arg-Trp-2-Aba-NH_2.

In compounds of formula II in which R^6 and R^8 are hydrogen; R^7 is 2-naphthyl i.e.



;

it is generally preferred that R^{10} is halo. Examples of such compounds include Penta-(D,L)-5-BrAtc-(D)Phe-Arg-(2)Nal-Gly-NH_2, 3-carboxylpropanoyl-(D,L)-5-BrAtc-(D)Phe-Arg-(2)Nal-Gly-NH_2, Phenylacetyl-(D,L)-5-BrAtc-(D)Phe-Arg-(2)Nal-Gly-NH_2 and Bu-(D,L)-5-BrAtc-(D)Phe-Arg-(2)Nal-2-Aba-NH_2.

Examples of compounds of formula III include Bu-Apc-(D)Phe-PhenylhomoArg-Trp-Gly-NH_2, Penta-Apc-(D)Phe-Cit-Trp-Gly-NH_2, Penta-Adpc-(D)Phe-Arg-Trp-Gly-NH_2 and Penta-Ape-(D)Phe-Arg-Trp-Gly-NH_2.

Preferred compounds as described above are those individually described in the examples.

Especially preferred compounds as described above are those selected from the group consisting of

Penta-Apc-(D)Phe-Arg-Trp-Gly-NH_2,

Penta-4-MeOApc-(D)Phe-Arg-Trp-Gly-NH_2,

Penta-4-EtOApc-(D)Phe-Arg-Trp-Gly-NH_2,
Bu-Apc-(D)Phe-Arg-(2)Nal-beta-Ala-NH_2,
Penta-Apc-(D)Phe-Cit-Trp-Gly-NH_2,
Penta-Abc-(D)Phe-Arg-Trp-Gly-NH_2,
Penta-Achc-(D)Phe-Arg-Trp-Gly-NH_2,
Penta-5-BrAtc-(D)Phe-Arg-Trp-Gly-NH_2,
Penta-Appc-(D)Phe-Arg-Trp-Gly-NH_2, and
Penta-4-MeAppc-(D)Phe-Arg-Trp-Gly-NH_2.

Compounds as described above are useful for the treatment and/or prophylaxis of diseases which are associated with melanocortin-4-receptor such as obesity. Consequently, the present invention relates to a pharmaceutical composition comprising a compound as described above and a pharmaceutically acceptable carrier and/or adjuvant. The present invention further relates to compounds as described above for use as therapeutic active substances, particularly as therapeutic active substances for the treatment and/or prophylaxis of diseases which are associated with melanocortin-4-receptor such as obesity. Another preferred embodiment of the present invention is a method for the treatment and/or prophylaxis of diseases which are associated with melanocortin-4-receptor such as obesity, which method comprises administering a compound as defined above to a human being or animal. The invention also relates to the use of compounds as described above for the treatment and/or prophylaxis of diseases which are associated with melanocortin-4-receptor such as obesity. The use of compounds as defined above for the preparation of medicaments for the treatment and/or prophylaxis of diseases which are associated with melanocortin-4-receptor such as obesity is a further preferred embodiment of the present invention. Such medicaments comprise a compound as described above.

Chemical Synthesis

The compounds of this invention can be readily synthesized by any known conventional procedure for the formation of a peptide linkage between amino acids. Such conventional procedures include, for example, any solution phase procedure permitting a

condensation between the free alpha amino group of an amino acid or residue thereof having its carboxyl group or other reactive groups protected and the free primary carboxyl group of another amino acid or residue thereof having its amino group or other reactive groups protected.

The synthesis of these compounds may be carried out by a procedure whereby each amino acid in the desired sequence is added one at a time in succession to another amino acid or residue thereof or by a procedure whereby peptide fragments with the desired amino acid sequence are first synthesized conventionally and then condensed to provide the desired peptide.

Such conventional procedures for synthesizing the novel compounds of the present invention include for example any solid phase peptide synthesis method. In such a method the synthesis of the novel compounds can be carried out by sequentially incorporating the desired amino acid residues one at a time into the growing peptide chain according to the general principles of solid phase methods [Merrifield, R. B., *J. Amer. Chem. Soc.* **1963**, *85*, 2149-2154; Barany *et al.*, The Peptides, Analysis, Synthesis and Biology, Vol. 2, Gross, E. and Meienhofer, J., Eds. Academic Press 1-284 (1980)].

Common to chemical syntheses of peptides is the protection of reactive side chain groups of the various amino acid moieties with suitable protecting groups, which will prevent a chemical reaction from occurring at that site until the protecting group is ultimately removed. Usually also common is the protection of the alpha amino group of an amino acid or fragment while that entity reacts at the carboxyl group, followed by the selective removal of the alpha amino protecting group and allow a subsequent reaction to take place at that site. While specific protecting groups are mentioned below in regard to the solid phase synthesis method, it should be noted that each amino acid can be protected by any protective group conventionally used for the respective amino acid in solution phase synthesis.

For example, alpha amino groups may be protected by a suitable protecting group selected from aromatic urethane-type protecting groups, such as benzyloxycarbonyl (Z) and

substituted benzyloxycarbonyl, such as *p*-chlorobenzyloxycarbonyl, *p*-nitrobenzyloxycarbonyl, *p*-bromobenzyloxycarbonyl, *p*-biphenyl-isopropoxycarbonyl, 9-fluorenylmethoxycarbonyl (Fmoc) and *p*-methoxybenzyloxycarbonyl (Moz); aliphatic urethane-type protecting groups, such as *t*-butyloxycarbonyl (Boc), diisopropylmethoxycarbonyl, isopropoxycarbonyl, and allyloxycarbonyl. Herein, Fmoc is the most preferred for alpha amino protection.

Guanidino groups may be protected by a suitable protecting group selected from nitro, p-toluenesulfonyl (Tos), Z, pentamethylchromanesulfonyl (Pmc), adamantyloxycarbonyl, and Boc. Pmc is the most preferred for arginine (Arg).

In the examples all solvents, isopropanol (iPrOH), methylene chloride (CH_2Cl_2), dimethylformamide (DMF) and N-methylpyrrolidinone (NMP) were purchased from Fisher or Burdick and Jackson and were used without additional distillation. Trifluoroacetic acid was purchased from Halocarbon or Fluka and used without further purification. Diisopropylcarbodiimide (DIC) and diisopropylethylamine (DIPEA) was purchased from Fluka or Aldrich and used without further purification. Hydroxybenzotriazole (HOBT) dimethylsulfide (DMS) and 1,2-ethanedithiol (EDT) were purchased from Sigma Chemical Co. and used without further purification. Protected amino acids were generally of the L configuration and were obtained commercially from Bachem, Advanced ChemTech, or Neosystem. Purity of these reagents was confirmed by thin layer chromatography, NMR and melting point prior to use. Benzhydrylamine resin (BHA) was a copolymer of styrene - 1% divinylbenzene (100-200 or 200-400 mesh) obtained from Bachem or Advanced Chemtech. Total nitrogen content of these resins were generally between 0.3 - 1.2 meq/g.

High performance liquid chromatography (HPLC) was conducted on a LDC apparatus consisting of Constametric I and III pumps, a Gradient Master solvent programmer and mixer, and a Spectromonitor III variable wavelength UV detector. Analytical HPLC was performed in reversed phase mode using Vydac C_{18} columns (0.4 x 30 cm). Preparative HPLC separations were run on Vydac columns (2 x 25 cm).

Peptides were prepared using solid phase synthesis following the principles and general method described by Merrifield, [*J. Amer. Chem. Soc.*, **1963**, *85*, 2149], although other equivalent chemical synthesis known in the art could be used as previously mentioned. Solid phase synthesis is commenced from the C-terminal end of the peptide by coupling a protected alpha-amino acid to a suitable resin. Such a starting material can be prepared by attaching an alpha-amino-protected amino acid by an ester linkage to a p-benzyloxybenzyl alcohol (Wang) resin, or by an amide bond between an Fmoc-Linker, such as p-[(R, S)-α-[1-(9H-fluoren-9-yl)-methoxyformamido]-2,4-dimethyloxybenzyl]-phenoxyacetic acid (Rink linker) to a benzhydrylamine (BHA) resin. Preparation of the hydroxymethyl resin is well known in the art. Fmoc-Linker-BHA resin supports are commercially available and generally used when the desired peptide being synthesized has an unsubstituted amide at the C-terminus.

In general, the amino acids or mimetics are coupled onto the Fmoc-Linker-BHA resin using the Fmoc protected form of amino acid or mimetic, with 2 - 5 equivalents of amino acid and a suitable coupling reagent. After couplings, the resin may be washed and dried under vacuum. Loading of the amino acid onto the resin may be determined by amino acid analysis of an aliquot of Fmoc-amino acid resin or by determination of Fmoc groups by UV analysis. Any unreacted amino groups may be capped by reacting the resin with acetic anhydride and diisopropylethylamine in methylene chloride.

The resins are carried through several repetitive cycles to add amino acids sequentially. The alpha amino Fmoc protecting groups are removed under basic conditions. Piperidine, piperazine or morpholine (20-40% v/v) in DMF may be used for this purpose. Preferably 40% piperidine in DMF is utilized

Following the removal of the alpha amino protecting group, the subsequent protected amino acids are coupled stepwise in the desired order to obtain an intermediate, protected peptide-resin. The activating reagents used for coupling of the amino acids in the solid phase synthesis of the peptides are well known in the art. For example, appropriate reagents for such syntheses are benzotriazol-1-yloxy-tri- (dimethylamino) phosphonium

hexafluorophosphate (BOP), Bromo-tris-pyrrolidino-phosphonium hexafluorophosphate (PyBroP), 2-(1H-Benzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (HBTU), and diisopropylcarbodiimide (DIC). Preferred here are HBTU and DIC. Other activating agents as described by Barany and Merrifield [The Peptides, Vol. 2, J. Meienhofer, ed., Academic Press, 1979, pp 1-284] may be utilized. Various reagents such as 1-hydroxybenzotriazole (HOBT), N-hydroxysuccinimide (HOSu) and 3,4-dihydro-3-hydroxy-4-oxo-1,2,3-benzotriazine (HOOBT) may be added to the coupling mixtures in order to optimize the synthetic cycles. Preferred here is HOBT.

The protocol for a typical synthetic cycle is as follows:

Protocol 1

Step	Reagent	Time
1	DMF	2 x 30 sec
2	40% piperidine/DMF	1 min
3	40% piperidine/DMF	15 min
4	DMF	2 x 30 sec
5	iPrOH	2 x 30 sec
6	DMF	3 x 30 sec
7	coupling	60 min - 18 hours
8	DMF	2 x 30 sec
9	iPrOH	1 x 30 sec
10	DMF	1 x 30 sec
11	CH_2Cl_2	2 x 30 sec

Solvents for all washings and couplings were measured to volumes of 10 - 20 ml/g resins. Coupling reactions throughout the synthesis were monitored by the Kaiser ninhydrin test to determine extent of completion [Kaiser *et at. Anal. Biochem.* **1970**, *34*, 595-598]. Slow reaction kinetics was observed for Fmoc-Arg (Pmc) and for couplings to secondary

amines by sterically hindered acids. Any incomplete coupling reactions were either recoupled with freshly prepared activated amino acid or capped by treating the peptide resin with acetic anhydride as described above. The fully assembled peptide-resins were dried in vacuum for several hours.

For each compound, the blocking groups were removed and the peptide cleaved from the resin by the following procedure. Generally, the peptide-resins were treated with 100 μL ethanedithiol, 100 μL dimethylsulfide, 300 μL anisole, and 9.5 mL trifluoroacetic acid, per gram of resin, at room temperature for 120 min. The resin is filtered off and the filtrates are precipitated in chilled ethyl ether. The precipitates are centrifuged and the ether layer is decanted. The residue was washed with two or three volumes of Et_2O and recentrifuged. The crude products are dried under vacuum.

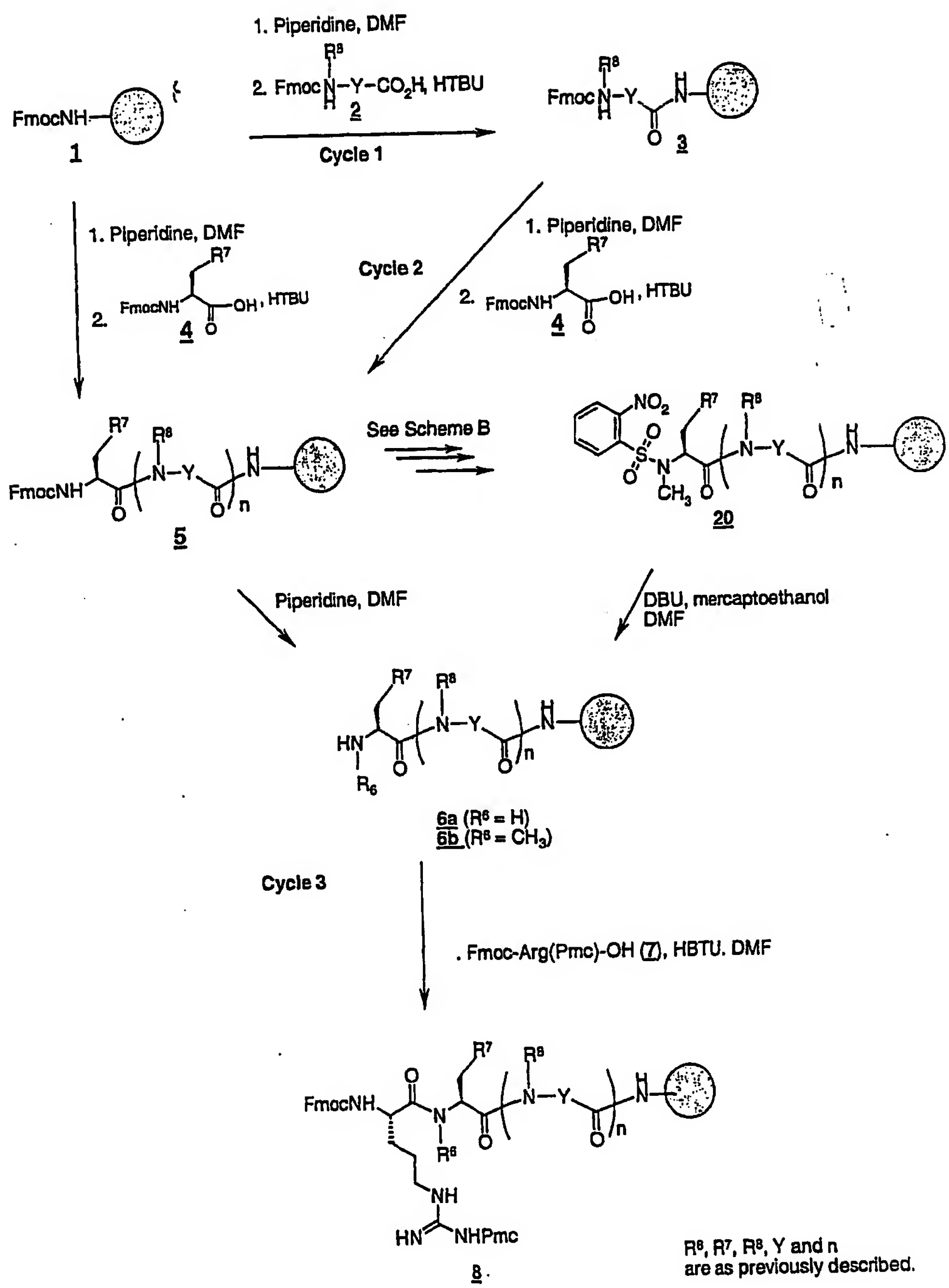
Purification of Crude Peptide Preparations

Purification of the crude peptides was carried out by preparative HPLC. The peptides were applied to the columns in a minimum volume of either $AcOH/H_2O$ or 0.1% TFA/H_2O. Gradient elution was generally started at 10% B buffer, 10% -60% B in 90 minutes, (buffer A: 0.1% TFA/H_2O, buffer B: 0.1% TFA/CH_3CN) at a flow rate of 8 mL/min. UV detection was made at 280 nm. Fractions were collected at 1.0 - 2.5 minute intervals and inspected by analytical HPLC. Fractions judged to be of high purity were pooled and lyophilized.

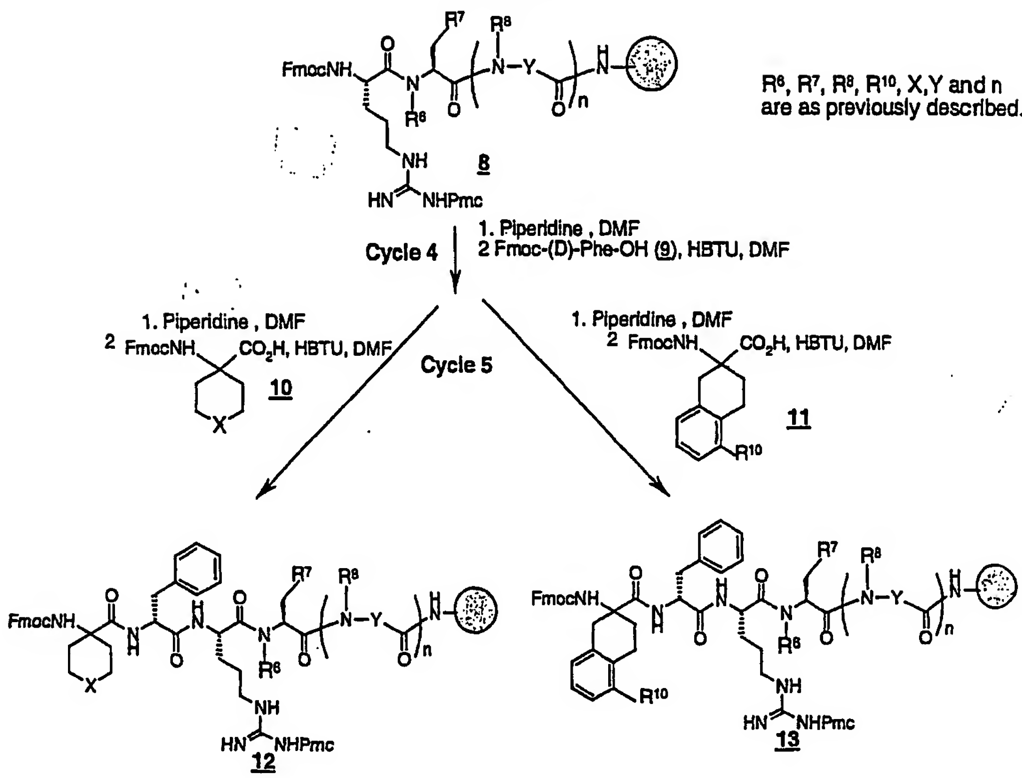
Purity of the final products was checked by analytical HPLC on a reversed phase column as stated above. Purity of all products was judged to be approximately 95 - 99%. All final products were also subjected to fast atom bombardment mass spectrometry (FAB-MS) or electrospray mass spectrometry (ES-MS). All products yielded the expected parent M+H ions within acceptable limits.

Utilizing the techniques described above, the compounds of this invention can be synthesized in accordance with the following reaction schemes.

Scheme A

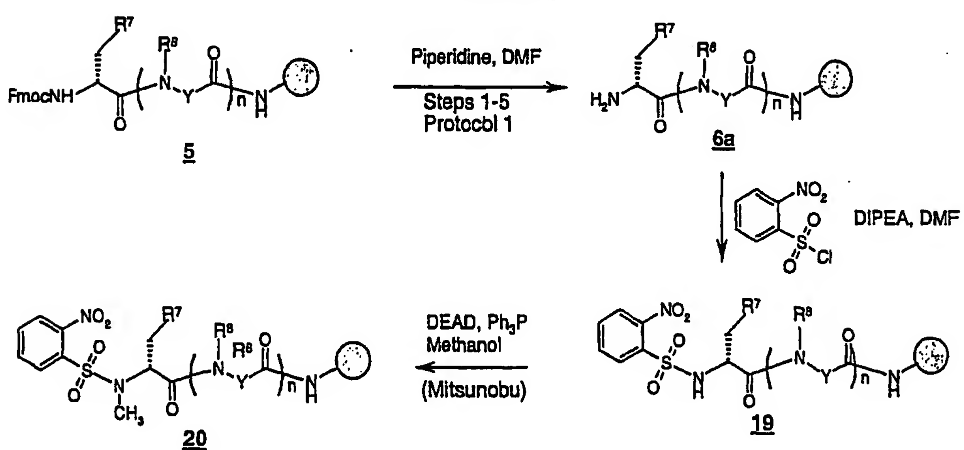

1. Piperidine, DMF
2. Fmoc N-Y-CO2H, HTBU
2
Cycle 1
FmocNH
1
3
1. Piperidine, DMF
2. FmocNH OH, HTBU
4
Cycle 2
5
See Scheme B
20
Piperidine, DMF
DBU, mercaptoethanol DMF
6a (R6 = H)
6b (R6 = CH3)
Cycle 3
. Fmoc-Arg(Pmc)-OH (7), HBTU. DMF
NHPmc
8
R6, R7, R8, Y and n are as previously described.

Scheme B



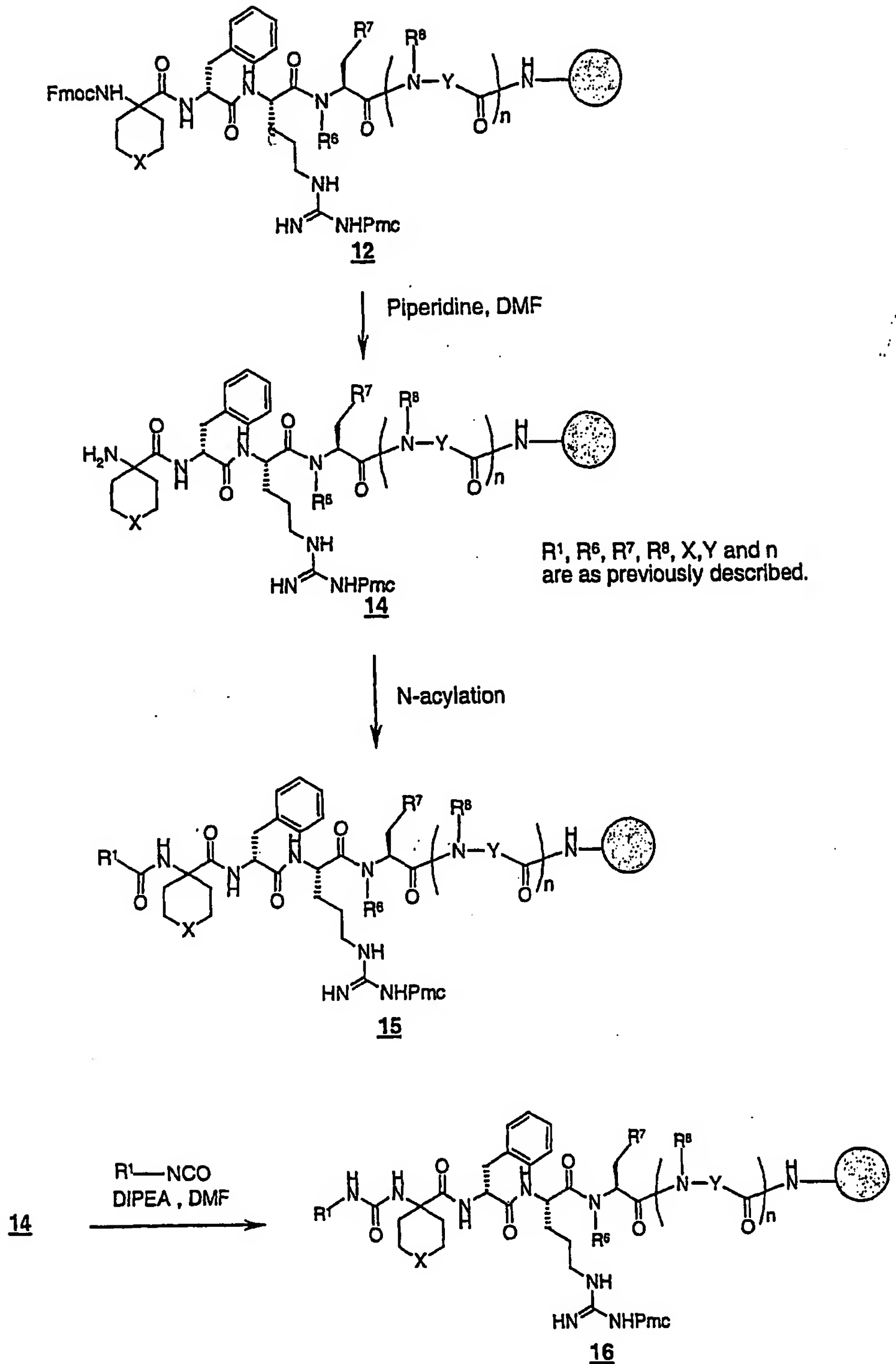
R^6, R^7, R^8, R^{10}, X,Y and n are as previously described.

Scheme C

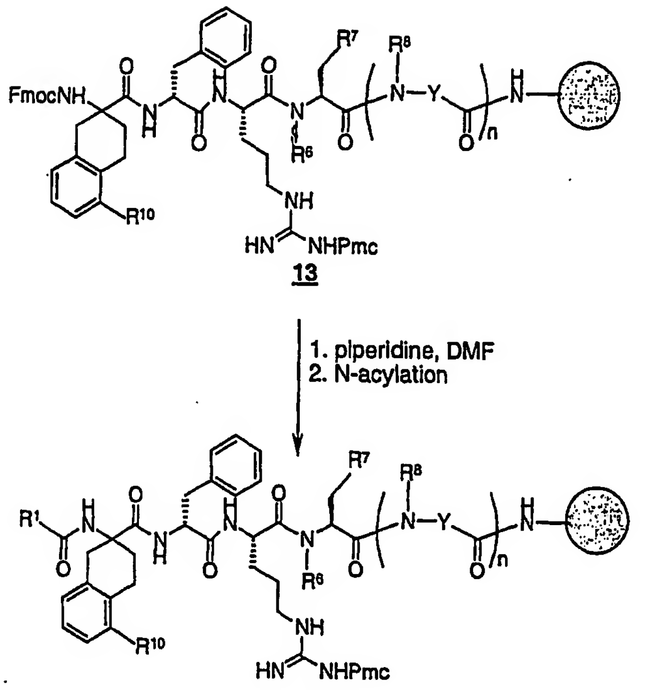


R^7, R^8, Y and n are as previously described.

Scheme D


12
Piperidine, DMF
14
R¹, R⁶, R⁷, R⁸, X,Y and n are as previously described.
N-acylation
15
14
R¹—NCO
DIPEA , DMF
16

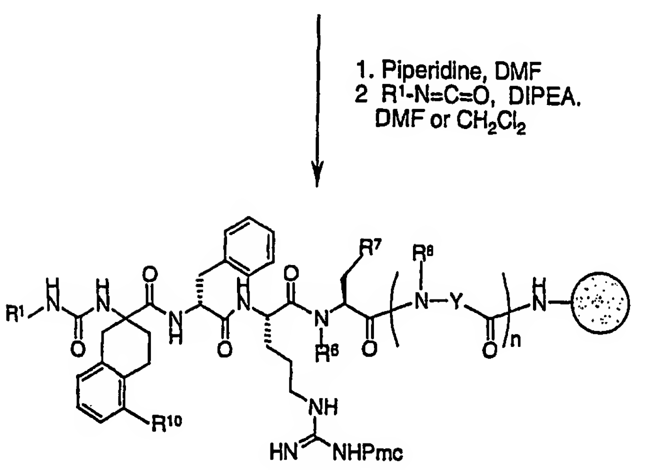
Scheme E



17

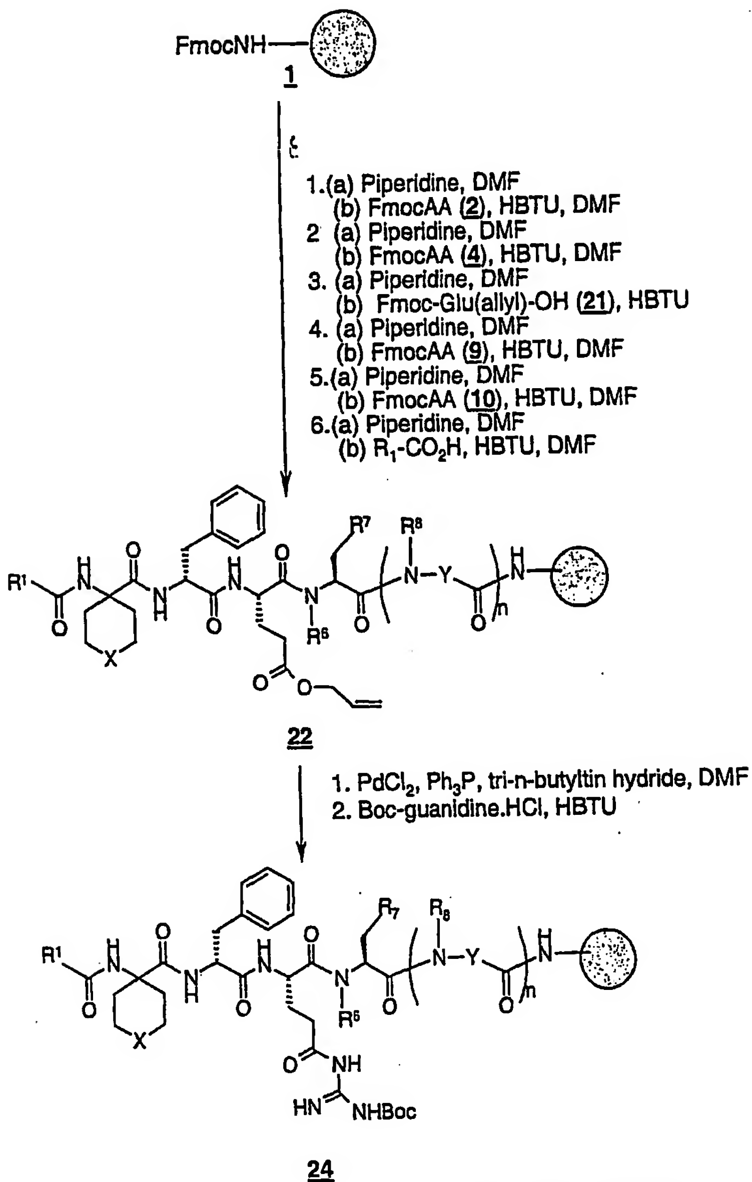
R^1, R^6, R^7, R^8, R^{10}, Y and n are as previously described.

13



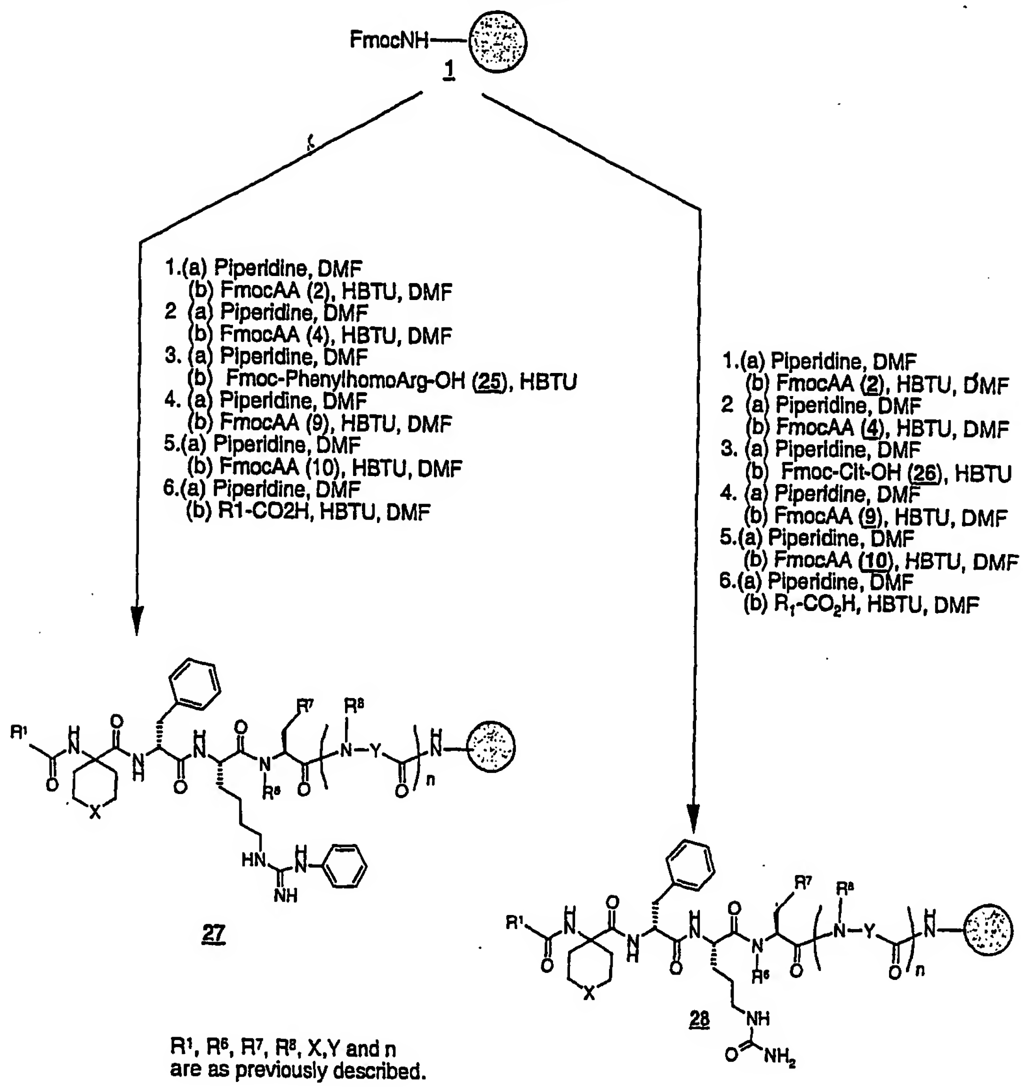
18

Scheme F



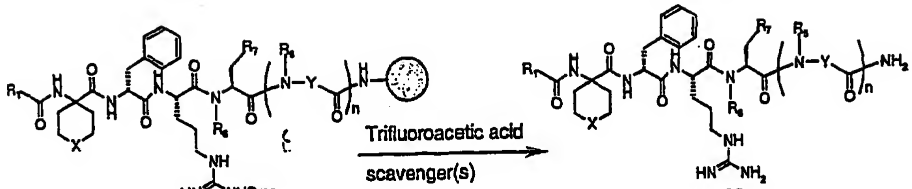
R¹, R⁶, R⁷, R⁸, X,Y and n are as previously described.

Scheme G

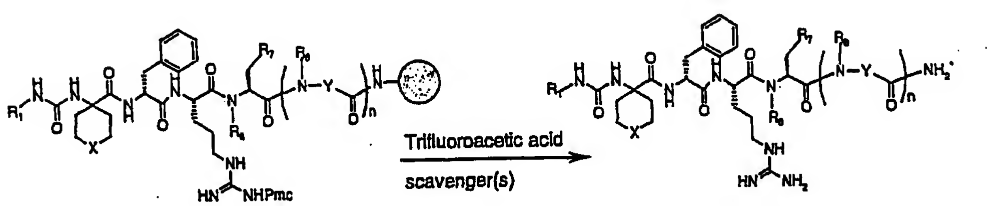


R¹, R⁶, R⁷, R⁸, X,Y and n are as previously described.

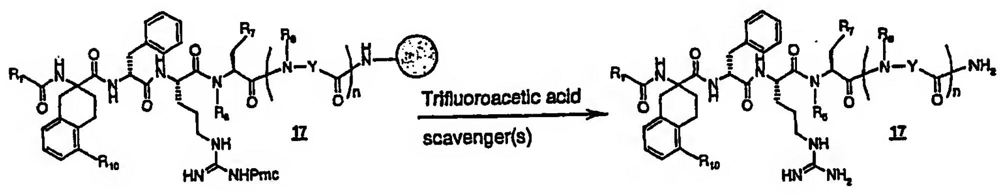
Scheme H



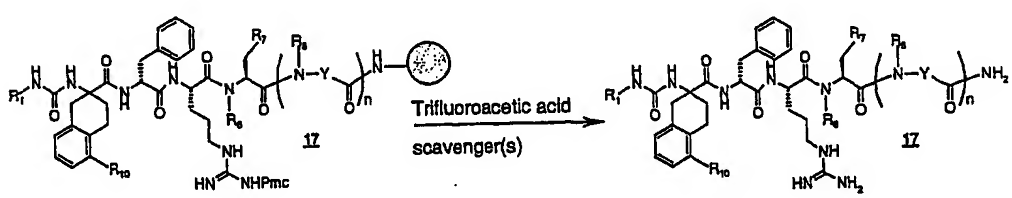
15 → 29



16 → 30



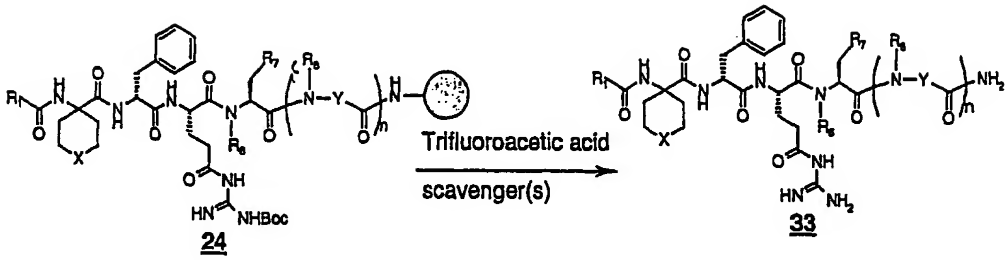
17 → 31

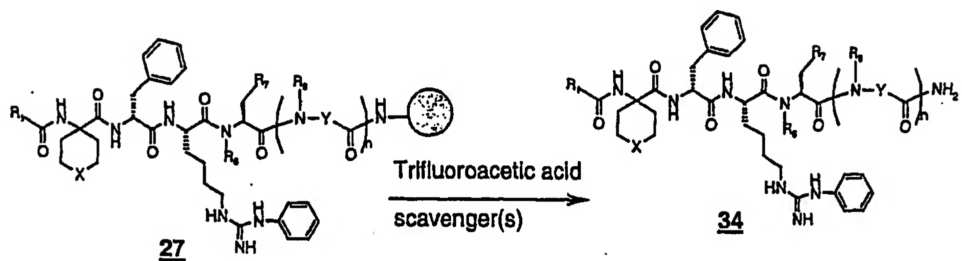


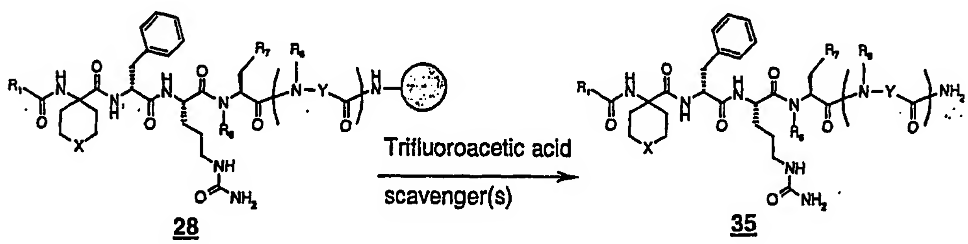
18 → 32

R_1, R_6, R_7, R_8, R_{10}, X,Y and n are as previously described.

Scheme H (cont.)

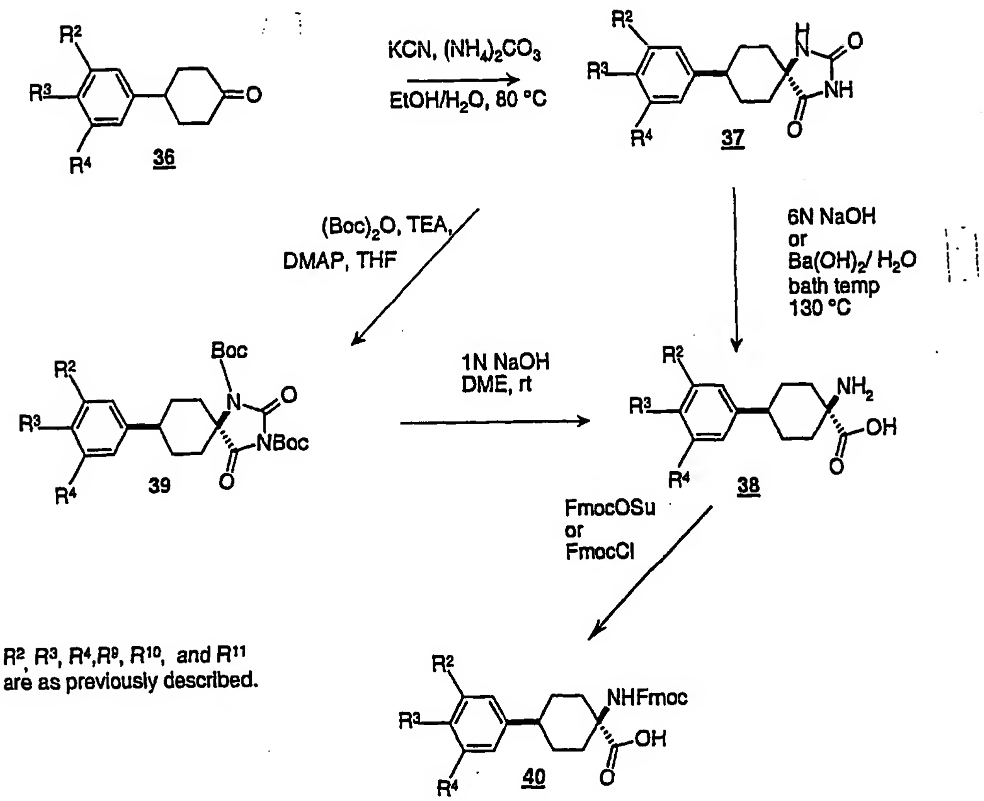




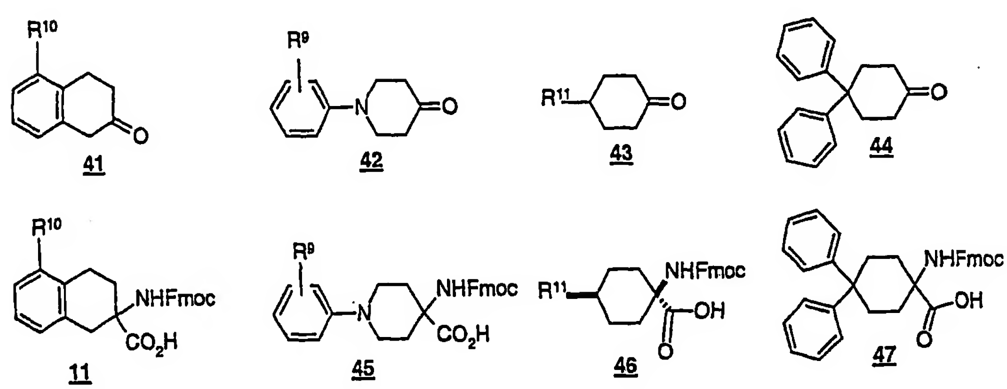


R_1, R_6, R_7, R_8, R_{10}, X,Y and n are as previously described.

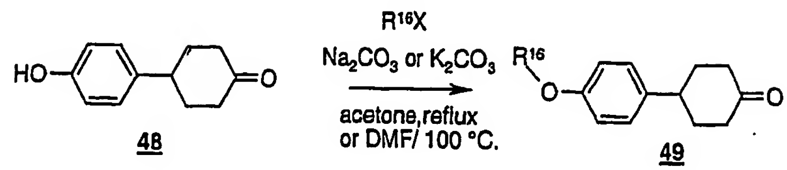
Scheme I



R², R³, R⁴, R⁹, R¹⁰, and R¹¹ are as previously described.

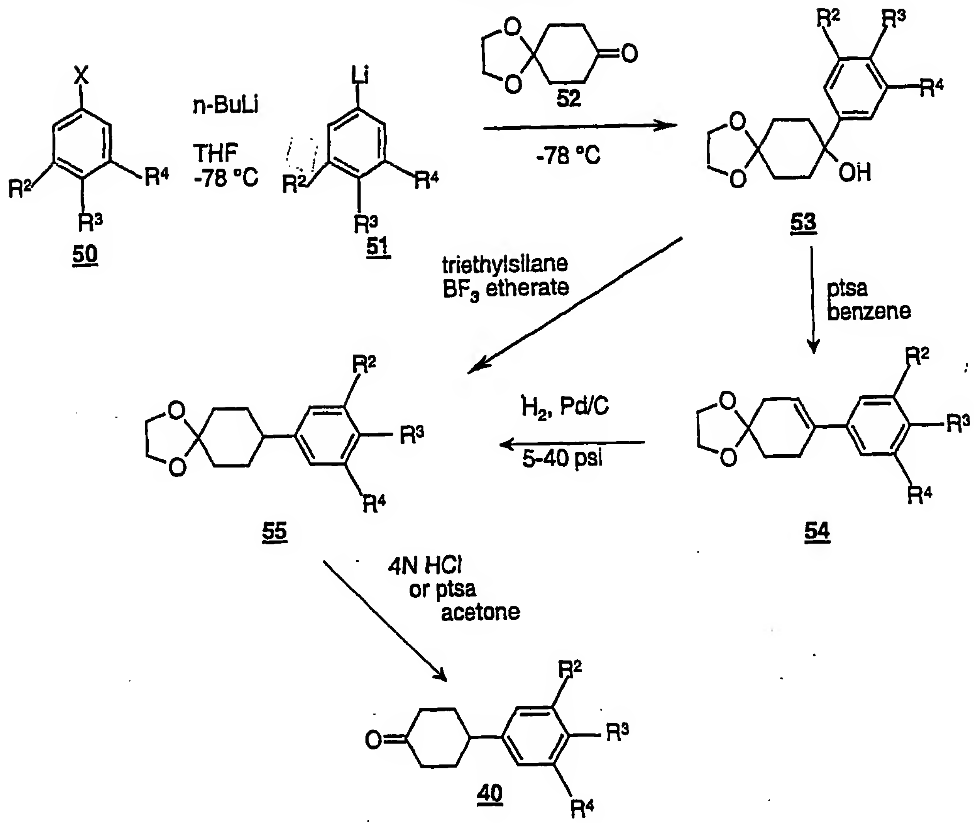


Scheme J



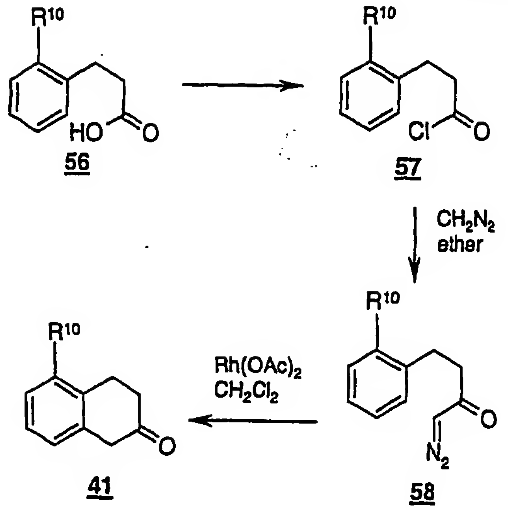
HO
O
48
$R^{16}X$
Na_2CO_3 or K_2CO_3
acetone,reflux
or DMF/ 100 °C.
R^{16}
O
O
49

Scheme K



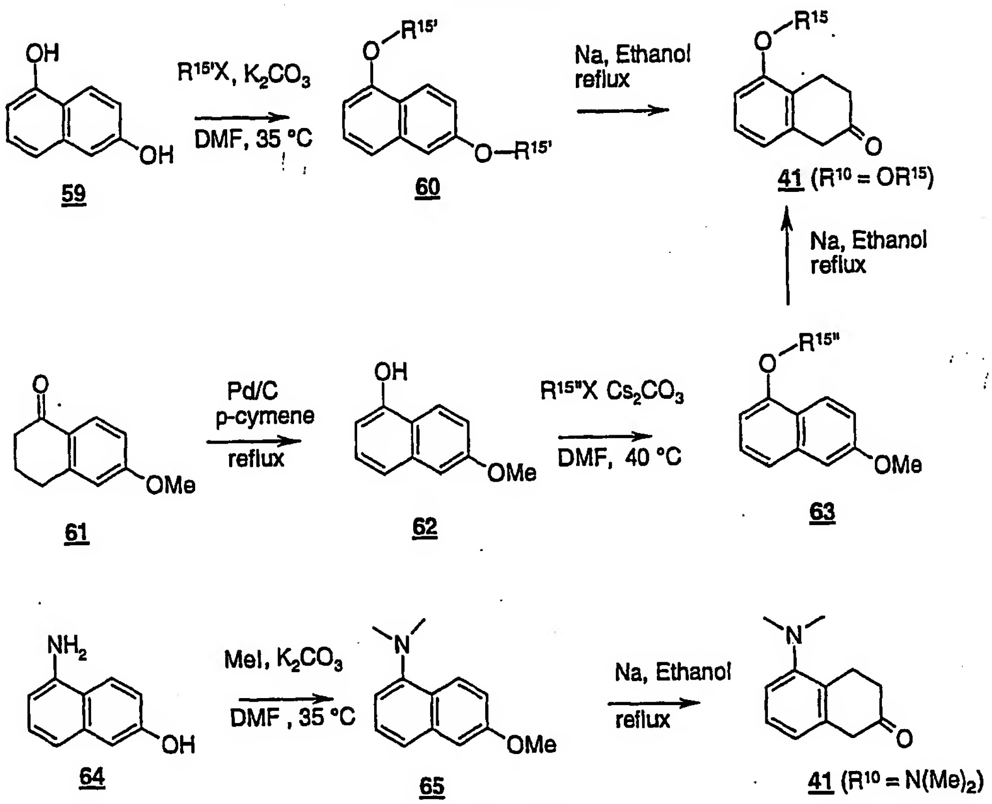
R^2, R^3 and R^4 are as previously described.

Scheme L



R^{10} is as previously described.

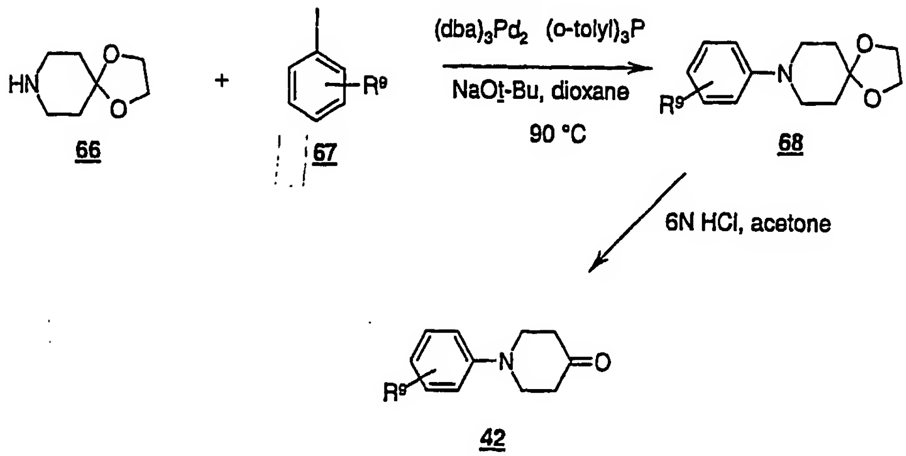
Scheme M



R

R^{10} is as previously described.

Scheme N



R^9 is as previously described.

The synthetic peptides of the current invention are prepared by using conventional solid phase peptide synthesis methodology discussed in the previous section. Each cycle consists of two procedures; the initial cleavage of the Fmoc protecting group from the terminal nitrogen in the resin bound chain followed by acylation of the amine function with an Fmoc protected amino acid. The cycle is generally carried out in accordance with the stepwsize procedures outlined in Protocol 1. The deprotection is accomplished by using an organic base, for example piperazine, morpholine or piperidine, preferably piperidine in a suitable inert solvent, for example N,N-dimethylformamide (DMF) or Nmethylpyrrolidone (NMP). The coupling reaction can be carried out by one of the many conditions developed for amide bond formation, for example O-benzotriazol-1-yl N,N,N',N'-tetramethyluronium hexafluorophosphate (HBTU) in the presence of an organic base, for example diisopropylethylamine (DIPEA) in an inert solvent, for example DMF. Alternatively in the present instance, the amide group can be formed using a carbodiimide, for example, diisopropylcarbodiimide (DIC) along with an activating agent such as 1-hydroxybenzotriazole (HOBT) in a suitable inert solvent such as DMF.

In **Scheme A**, in the first cycle, the Fmoc-Linker-BHA Resin represented by structure 1 is deprotected and condensed with Fmoc-amino acids of structure 2 to give the resin bound compounds of structure 3. A second cycle incorporates the Fmoc-amino acids 4 to give the compounds of structure 5 ($n = 1$). Compounds of structure 5 in which $n = 0$ are prepared by eliminating the first cycle, and by coupling Fmoc-amino acids of structure 4 directly to the deprotected Fmoc-Linker-BHA Resin. In the third cycle, treatment of the resin linked peptide furnishes the intermediates of structure 6a where R^6 represents hydrogen. The intermediates of structure 6b where R^6 represents methyl are synthesized as shown in **Scheme C**. Compounds of structure 6a, prepared by treating compounds of structure 5 as prescribed in steps 1-5 of Protocol 1, are reacted with an arylsulfonyl chloride, preferably 2-nitrobenzenesulfonyl chloride. The reaction is carried out in the presence of a proton acceptor, for example pyridine, triethylamine (TEA) or DIPEA, preferably DIPEA in a suitable inert solvent, preferably DMF. N-methylation of the formed sulfonamide group in the washed resin bound compounds of structure 19 is accomplished under Mitsunobu

conditions. Thus the sulfonamides of structure 19 are reacted with methanol in the presence of diethyl azodicarboxylate (DEAD) and triphenylphosphine using methanol as solvent. After the reaction is complete, the resin bound N-methylsulfonamide of structure 20 is washed free of residual reagents and byproducts. The 2-nitrobenzenesulfonyl residue is removed by reacting 20 with 2-mercaptoethanol and the strong organic base 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in a suitable solvent, preferably DMF to give the resin bound intermediate of structure 6b. The third cycle is completed by coupling compounds of either structures 6a and 6b with Fmoc-Arg(Pmc)-OH (7) to give the resin bound compounds of structure 8. Two additional cycles (**Scheme B**) are carried out on peptides of structure 8 where the amino acid Fmoc-(D)-Phe-OH (9) followed by either one of the amino acid derivatives of structure 10 or 11 are sequentially incorporated into the resin bound peptide to give the resin bound polypeptides of structures 12 and 13.

Removal of the Fmoc from the resin bound polypeptides 12 is carried out by treatment of 12 with piperidine in DMF to give the compounds of structure 14 using the reaction conditions outlined in Steps 1-5 of Protocol 1. The polypeptide is then N-capped by reaction with an acylating agent to form the resin bound amides of structure 15 or by reaction with an isocyanate to form the ureas of structure 16 (**Scheme D**). The acylation is carried out under a variety of methods well known to one skilled in the art. Among the methods used are:

(i) reaction of the compounds of structure 14 with a carboxylic acid R^1-CO_2H in a suitable solvent, such as DMF in the presence of HBTU, and an organic base, preferably DIPEA and

(ii) reaction of the compounds of structure 14 with a carboxylic acid chloride R^1-COCl in a suitable solvent, such as dichloromethane in the presence an organic base, such as pyridine, TEA and DIPEA, preferably DIPEA and

(iii) reaction of the compounds of structure 14 with a carboxylic acid anhydride (R^1-CO_2CO-R^1 in a suitable solvent, such as dichloromethane or DMF in the presence an organic base, preferably DIPEA.

The reaction of the compounds of structure 14 with an isocyanate R^1-NC0 is carried out in a suitable solvent, such as dichloromethane or DMF in the presence an organic base, preferably DIPEA.

When the acylation and urea forming reactions are complete, the resin bound products 15 and 16 are washed free of residual reagents and byproducts.
Using the same conditions, the resin bound polypeptides of structure 13 are converted to the N-acylated compounds of structure 17 and the ureas of structure 18 (**Scheme E**).
In **Scheme F**, the sequencing is carried out as in **Scheme A** except that Fmoc-Glu(allyl)-OH (21) is incorporated into the resin bound polypeptide instead of Fmoc-Arg(Pmc)-OH (7) to give the resin bound N-capped polypeptides of structure 22. The allyl group is removed by treatment of 22 with tributyltin hydride, palladium chloride and triphenylphosphine in an inert solvent, for example DMF to give the resin bound polypeptide of structure 23. Coupling of 23 with Boc-guanidine gave the acylguanidine resin bound compounds of structure 24. The reaction can be carried out by using standard amide forming reaction methods, for example in the presence of HBTU and an organic base, preferably DIPEA in a suitable solvent, such as DMF.

In **Scheme G**, the sequencing is carried out as in **Scheme A** except that either Fmoc-PhenylhomoArg-OH (25) or Fmoc-citrulline (26) is incorporated into the resin bound polypeptide in the place of Fmoc-Arg(Pmc)-OH (7) to give the resin bound N-capped polypeptides of structures 27 and 28 respectively.

As shown in **Scheme H**, the cleavage of remaining protecting groups in the N-capped polypeptides 15-18, 24, 27 and 28 and the concomitant cleavage of the peptides from the solid support is carried out by using a strong organic acid, preferably trifluoroacetic acid, optionally in the presence of an inert solvent such as dichloromethane and a trace (1%) of water. The reaction is conveniently carried out with or without the presence of one or more carbocation scavengers, for example ethanedithiol, dimethyl sulfide, triethylsilane and anisole. The polypeptide cleavage solution is filtered free from the solid support, then is diluted with a suitable solvent, preferably diethyl ether. The solid polypeptides of structures 29-35 produced in this manner is purified by reversed phase chromatography over a

preparative C18 column. If convenient, in those cases where a racemic Fmoc-amino acid 11 is sequenced into the polypeptide, the individual stereoisomers are separated during the purification procedure. The Fmoc-amino acids 2, 4, 7, 9, 21, 25 and 26 as well as the acylating agents and isocyanates used to N-cap the polypeptides are known compounds that are commercially available.

The Fmoc-amino acids 10 and 11 are prepared as described herein by methods that are well known to those of ordinary skill in the practice of organic chemistry. In **Scheme I**, the preparation of Fmoc-amino acids from cyclic ketones is outlined. The 4-phenylcyclohexanones of formula 36 are converted to the hydantoins of formula 37 by treatment with ammonium carbonate and potassium cyanide. The reaction is conveniently carried out an aqueous ethanol mixture at a temperature of from 50 ^{0}C to 90 ^{0}C, preferably between 80 ^{0}C and 90 ^{0}C. Direct hydrolysis of the hydantoins to the amino acids of structure 38 require a prolonged treatment with strong base, for example with 6N sodium hydroxide solution or with barium hydroxide at reflux temperature. Alternatively, compounds of structure 37 can be converted to the bis-Boc derivatives of structure 39. The reaction is carried out using tert-butyl dicarbonate [$(Boc)_2O$] in an inert solvent, preferably tetrahydrofuran (THF), in the presence of an organic amine base, preferably TEA and a catalyst, 4-dimethylaminopyridine (DMAP) at a temperature of from zero degrees to room temperature, preferably at room temperature. The bis-Boc hydantoins of structure 39 are readily converted to the amino acids of structure 38. The reaction is accomplished using 1N sodium hydroxide in an inert solvent, preferably dimethoxyethane (DME) at from zero degrees to 50 ^{0}C, preferably at about room temperature. Protection of the amino functionality with an Fmoc group in a compound of structure 38 is carried out under a variety of reaction conditions to give 40. The reaction may conveniently be performed by treatment of a solution of the amino acid 38 in a mixture of THF or dioxane, preferably dioxane and aqueous sodium carbonate with 9-fluorenylmethoxychloroformate (FmocCl) at a temperature of from zero degrees to room temperature, preferably at room temperature. Alternatively, N-(9-fluorenylmethoxycarbonyloxy)succinimide (FmocOSu) is added to a solution of the amino acid 38 in aqueous acetonitrile containing an organic tertiary amine base, preferably TEA. The reaction is run at from zero degrees to room temperature, preferably at room

temperature. In another variation of the procedure, DME is evaporated from the hydrolysis mixture in the conversion of 39 to 38 and the reaction is adjusted to ~pH 11. The resulting solution of the sodium salt of 38 is then treated *in situ* with FmocOSu or FmocCl in dioxane at a temperature of from zero degrees to room temperature, preferably at room temperature.

In the same manner, the tetralones 41, the N-aryl-4-ketopiperidines 42, and the cyclohexanone derivatives 43 and 44 are converted to the corresponding Fmoc-amino acids of structures 11 and 45-47.

Compounds of structure 40 where R^3 represents a linear or branched lower alkoxy and R^2 and R^4 is hydrogen, as in the sub genus structure 49, may be prepared by 0-alkylation of the compound of structure 48 (**Scheme J**). Where R^{16} represents an unbranched lower alkyl moiety, the alkylation is carried out by using a primary alkyl halide of structure $R^{16}X$ in the presence of an alkali metal carbonate, for example, sodium or potassium carbonate. The alkyl halide may be a chloro, bromo or iodo derivative, preferably an alkyl iodide (X = I). The reaction may be conveniently carried out in an inert solvent that promotes Sn2 displacement reactions, for example acetone, 2-butanone or N,N-dimethylformamide, preferably acetone, at a temperature of from room temperature to the reflux temperature of the solution, preferably the reflux temperature. When R^{16} represents a branched lower alkyl group, e.g., 2-propyl, the alkylation is carried out by using a secondary alkyl halide of structure $R^{16}X$ in the presence of an alkali metal carbonate, e.g., potassium carbonate. The secondary alkyl halide is preferably a secondary alkyl iodide, for example, 2-iodopropane (X = I). The reaction may be conveniently carried out in an inert solvent, preferably N,N-dimethylformamide, at a temperature of from room temperature to the reflux temperature of the solution, preferably at about 100 °C.

Compounds of structure 40 can be prepared by methods that are well known to one of ordinary skill in the practice of organic chemistry. As outlined in **Scheme K**), treatment of the aryl halides of structure 50 (X' represents bromo or iodo) with an alkyl metal reagent, preferably t-butyl lithium, results in a transmetalation reaction to give the corresponding aryl lithium of structure 51. The reaction is conveniently carried out at -78 °C by the addition of a

solution of the alkyl lithium in to a solution of compounds of structure <u>50</u> an inert anhydrous solvent, such as diethyl ether or tetrahydrofuran, preferably tetrahydrofuran. The aryl lithium of structure <u>51</u>, is then reacted *in situ* with a solution of the monoketal of cyclohexane-1,4-dione (<u>52</u>) in an suitable inert solvent, for example tetrahydrofuran, while the reaction temperature is maintained below -60 °C, preferably at about -78 °C to give the carbinols of structure <u>53</u>. The compounds of structure <u>54</u> are obtained by the dehydration of the carbinols of structure <u>53</u>. The reaction is conveniently carried out using a strong organic acid catalyst, preferably p-toluenesulfonic acid in an inert solvent, for example benzene or toluene, preferably benzene, at the reflux temperature of the solvent. The formed water is removed from the reaction mixture by means of a Dean Stark apparatus to enable the reaction to go to completion. Compounds of structure <u>55</u> are produced by hydrogenation of the olefins of structure <u>54</u>. The reaction is conveniently carried out using a noble metal catalyst, for example palladium on carbon, in a hydrogen atmosphere in an inert solvent, for example ethanol or ethyl acetate. The hydrogenation is usually carried out at room temperature and 40 psi of hydrogen, however if the aryl ring in structure <u>54</u> contains a group prone to hydrogenolysis, e.g., if R^2, R^3 or R^4 represents chloro, the reaction pressure is kept at about 5 psi. Compounds of structure <u>55</u> may be also obtained directly from carbinols of structure <u>53</u> by reductive elimination of the hydroxyl group. In this reaction a solution of the compound of structure <u>53</u> ($R^2 = R^3$ =H and R^4 = OMe) in an inert solvent, for example dichloromethane, is treated with a Lewis acid, such as boron trifluoride etherate, and a reducing agent, for example triethylsilane, at a temperature of from zero degrees to room temperature. Removal of the ketal protectimg group in compounds of structure <u>55</u> gives the ketone of formula <u>40</u>. The reaction is conveniently carried out in acetone or 2-butanone, preferably acetone under acid catalysis, for example 4N hydrochloric acid or p-toluenesulfonic acid at from room temperature to the reflux temperature of the reaction mixture, preferably at the reflux temperature.

5-Substituted-beta-tetralones of structure <u>41</u> are generally known compounds, or if they are not known they can be prepared by methods that are well known to one of ordinary skill in the field of organic chemistry. In the present instance, compounds of structure <u>41</u> are prepared by two methods outlined in **Schemes L** and **M**.

As shown in **Scheme L**, a 2-substituted hydrocinnamic acid of structure 56 (R^{10} = bromo, chloro or a linear or branched alkyl group of from 1 to 3 carbons) is converted to the corresponding carboxylic acid chloride of structure 57. This conversion can be carried out by several methods, for example by treatment of the hydrocinnamic acid with oxalyl chloride, optionally in the presence of a catalytic amount of N,N-dimethylformamide, in an inert solvent, such as benzene or dichloromethane, preferably dichloromethane. The reaction may be conveniently carried out at a temperature of from zero degrees to room temperature, preferably at room temperature. Alternatively the compound of structure 56 is reacted with an acyl chloride forming reagent such as sulfuryl chloride in an inert solvent, for example benzene or toluene, preferably toluene at a temperature between room temperature to the reflux temperature of the solution, preferably at the reflux temperature.

The diazoketone of structure 58 is prepared by treatment of the thus formed acyl halide of structure 57 in an inert solvent, e.g., dichloromethane with an excess of a freshly prepared ethereal solution of diazomethane. The combination of reagents is conveniently carried out at ice bath temperature and the reaction is then allowed to proceed at a temperature of from zero degrees to room temperature, preferably at room temperature. Cyclization of the diazoketone of structure 58 to furnish the tetralone of structure 41 is promoted by rhodium (II) acetate dimer in an inert solvent, e.g., dichloromethane. The reaction is normally carried out at from room temperature to the reflux temperature of the solution, preferably at the reflux temperature.

Compounds of structure 41, wherein R^{10} represents a linear or branched lower alkoxy group or a dialkylamino substituent, are prepared as shown in **Scheme M**. The compounds of structure 60 ($R^{15'}$= an unbranched lower alkyl moiety) are prepared by per-O-alkylation of the naphthalenediol of structure 59 with a primary alkyl iodide or bromide, preferably an iodide, in the presence of a base such as an alkali metal carbonate, for example, sodium or potassium carbonate. The reaction may be carried out in an inert solvent, preferably N,N-dimethylformamide at a temperature of from room temperature to 100 °C, preferably at 35°C. The compounds of structure 63 ($R^{15''}$ represents a branched lower alkyl) are prepared in two steps from the 2-tetralone of structure 61. The tetralone of structure 61 is subjected to

dehydrogenation in the presence of a noble metal catalyst, such as palladium metal (10% on carbon) in a suitable high boiling solvent such as p-cymene to give the aromatized compound of structure 62. The naphthol of structure 62 is then 0-alkylated with a secondary alkyl iodide in the presence of a base such as an alkali metal carbonate, preferably cesium carbonate to furnish the compound of structure 63. The reaction may be conveniently carried out in an inert solvent, preferably N,N-dimethylformamide at a temperature of from room temperature to 100 °C, preferably at about 40 °C. The compound of structure 65 is prepared by alkylation of 5-amino-2-naphthol (64) with methyl iodide in the presence of a base such as an alkali metal carbonate, preferably potassium carbonate. The reaction may be carried out in an inert solvent, for example acetone or 2-butanone, preferably acetone, at a temperature between room temperature and the reflux temperature of the solution, preferably at the reflux temperature.

The tetralones of structures 41 are produced by reduction of the compounds of structures 60, 63 and 65 under dissolving metal conditions, followed by the acid catalyzed hydrolysis of the intermediate enol ethers. The transformation is conveniently carried out by the portionwise addition of a large excess of an alkali metal, such as sodium or potassium, preferably sodium, to a boiling solution of the substrate in an lower alcohol, preferably alcohol until the starting material is consumed. The tetralones of structures 41 are obtained by treatment of a solution of the isolated intermediate enol ethers with a strong acid catalyst, preferably p-toluenesulfonic acid. The hydrolysis may conveniently carried out in a mixture of a lower alcohol, preferably ethanol, and water at a temperature of between room temperature and the reflux temperature of the solution, preferably at the reflux temperature.

Compounds of structure 68 are can be prepared by reactions that are known per se. For example, they can be prepared by coupling a secondary amine of structure 66 with an aryl bromide or iodide, preferably an aryl iodide of structure 67 (**Scheme N**). The coupling reaction is catalyzed by a noble metal catalyst, preferably tri(dibenzylideneacetone)-dipalladium, in the presence of a chelating phosphine ligand, preferably tri-o-tolylphosphine, and a hindered alkoxide base such as sodium tert-butoxide. The reaction is conveniently carried out in an inert atmosphere using an anhydrous solvent such as dioxane or toluene,

preferably dioxane, at a temperature of from 60 °C to the reflux temperature, preferably at 90 °C. Compounds of structure 56 and 66 are generally known compounds and are can be obtained from commercial sources. Removal of the carbonyl protecting group in compound 67 to give compounds of structure 42 can be carried out by a variety of methods well known in the field of organic chemistry. For example, the deprotection can be achieved by treatment of a solution of compound 68 in a low boiling ketone such as acetone or 2-butanone with an aqueous mineral acid solution, for example 6N hydrochloric acid. The reaction can be run at a temperature of from room temperature to the reflux temperature of the mixture, preferably at the reflux temperature.

The cyclohexanone derivatives of structures 63 are commercially available compounds and the 4,4-diphenylcyclohexanone (64) is prepared by published procedures.

The invention also relates to a process for the preparation of compounds as described above, which process comprises cleaving a compound as described above which is bound to a solid support from said solid support with an acid. Such processes are described above, e.g. in scheme H and are also well known to the person skilled in the art, e.g. also from literature cited in this specification. Preferably, the acid with which the above mentioned cleavage is performed, is trifluoroacetic acid. The cleavage can be carried out in a solvent such as e.g. dichloromethane with an optional trace (about 1 %) of water. The cleavage can be carried out with a scavenger such as e.g. ethaneditiol, dimethyl sulfide, triethylsilane or anisole. Suitable solid supports are well known to the person skilled in the art e.g. from literature cited in this specification and are also commercially available. The preparation of compounds as defined above which are bound to a solid support is described e.g. in the schemes above and in the examples. Protecting groups can be removed, e.g. a Pmc group from a guanidino group, at the same time during the above mentioned cleavage. The invention further relates to compounds as defined above, when manufactured by a process as defined above.

The compounds as described above can be used as medicaments, e.g. in the form of pharmaceutical preparations for enteral, parenteral or topical administration. They can be administered, for example, perorally, e.g. in the form of tablets, coated tablets, dragées, hard

and soft gelatine capsules, solutions, emulsions or suspensions, rectally, e.g. in the form of suppositories, parenterally, e.g. in the form of injection solutions or infusion solutions, or topically, e.g. in the form of ointments, creams or oils.

The production of the pharmaceutical preparations can be effected in a manner which will be familiar to any person skilled in the art by bringing the compounds as described above, optionally in combination with other therapeutically valuable substances, into a galenical administration form together with suitable, non-toxic, inert, therapeutically compatible solid or liquid carrier materials and, if desired, usual pharmaceutical adjuvants.

Suitable carrier materials are not only inorganic carrier materials, but also organic carrier materials. Thus, for example, lactose, corn starch or derivatives thereof, talc, stearic acid or its salts can be used as carrier materials for tablets, coated tablets, dragées and hard gelatine capsules. Suitable carrier materials for soft gelatine capsules are, for example, vegetable oils, waxes, fats and semi-solid and liquid polyols (depending on the nature of the active ingredient no carriers are, however, required in the case of soft gelatine capsules). Suitable carrier materials for the production of solutions and syrups are, for example, water, polyols, sucrose, invert sugar and the like. Suitable carrier materials for injection solutions are, for example, water, alcohols, polyols, glycerol and vegetable oils. Suitable carrier materials for suppositories are, for example, natural or hardened oils, waxes, fats and semi-liquid or liquid polyols. Suitable carrier materials for topical preparations are glycerides, semi-synthetic and synthetic glycerides, hydrogenated oils, liquid waxes, liquid paraffins, liquid fatty alcohols, sterols, polyethylene glycols and cellulose derivatives.

Usual stabilizers, preservatives, wetting and emulsifying agents, consistency-improving agents, flavour-improving agents, salts for varying the osmotic pressure, buffer substances, solubilizers, colorants and masking agents and antioxidants come into consideration as pharmaceutical adjuvants.

The dosage of the compounds as described above can vary within wide limits depending on the disease to be controlled, the age and the individual condition of the patient

and the mode of administration, and will, of course, be fitted to the individual requirements in each particular case. For adult patients a daily dosage of about 1 mg to about 1000 mg, especially about 10 mg to about 500 mg, comes into consideration. Depending on the dosage it is convenient to administer the daily dosage in several dosage units.

The pharmaceutical preparations conveniently contain about 1-500 mg, preferably 5-200 mg, of a compound as described above.

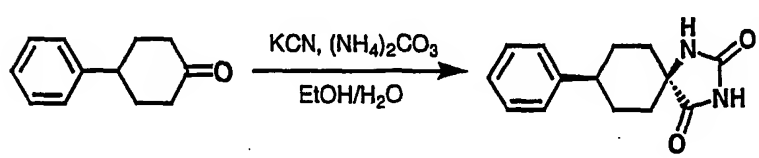
This invention will be better understood by reference to the following examples, which illustrate but do not limit the invention described herein.

EXAMPLE 1

Preparation of

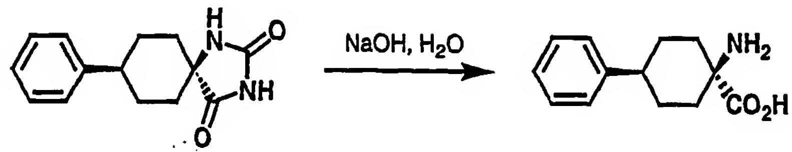
Fmoc-1-amino-4-phenylcyclohexane-1-carboxylic acid (**Fmoc-Apc-OH**)

Step 1:



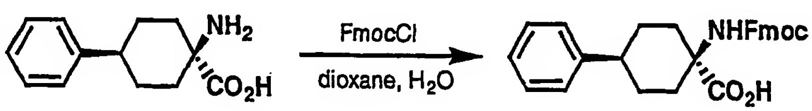
To a solution of 4-phenylcyclohexanone (10.0 g, 57.5 mmol) in ethanol (100 mL) and water (33 mL) in a glass pressure bottle, were added ammonium carbonate (33 g, 344 mmol, 6 equiv.) and potassium cyanide (5.6 g, 86.2 mmol, 1.5 equiv.). The mixture was heated at 80-90 ^{0}C for 24 hrs. The cooled reaction mixture was added to icy water (400 ml) and stirred vigorously for 30 min. The resulting precipitate was suction filtered, washed thoroughly with water and dried to yield the hydantoin as a white solid (14.0 g, 100% yield). ^{1}H NMR (DMSO-d_6): 8.63 (s, 1H), 7.23-7.36 (m, 4), 7.15 (m, 1), 2.50 (m, 1H), 2.10 (m, 1H), 1.85 (d, 1H) and 1.55-1.80 (m, 6H).

Step 2:



The hydantoin (10.0 g) was suspended in aqueous NaOH (6N, 350 mL) and heated at 130 °C for 2-3 days. Upon the completion of the hydrolysis, the reaction mixture was neutralized with conc. HCl to slightly acidic (pH ~6). The resulting slurry was filtered, washed with water and dried to give 1-amino-4-phenylcyclohexane carboxylic acid (APC) as a white solid (25 g, >100 % yield. contaminated with inorganic salt) which was used directly for next step. Small portion of the crude product was purified on HPLC. ^{1}H NMR (DMSO-d_6): 7.23~7.7.35 (m,2), 7.10-7.19 (m, 3H), 2.45 (m, 1H), 1.92-2.18 (m, 3H), 1.56-1.78 (m, 4H) and 1.20 (m, 1H); LRMS (electrospray) *m/e* 220 (M+1)$^+$, Calcd for $C_{13}H_{17}NO_2$, 219.

Step 3:



The crude APC from the last step (25 g) was treated with Fmoc-Cl (13.2 g., 1.25 equiv) in dioxane (300 mL) and aqueous 10 % Na_2CO_3 (150 ml) and stirred vigorously overnight. The reaction mixture was concentrated to remove dioxane, neutralized with 6N HCl to slightly acidic (pH 5-6) and extracted with EtOAc. The combined organic extracts were washed with brine and dried over Na_2SO_4. Removal of the solvent gave the crude product which was then purified on flash chromatography (hexane/EtOAc to CH_2Cl_2/MeOH) to give pure Fmoc-*cis*-APC (18.2 g, 72% overall yield for two steps) and Fmoc-*trans*-APC (2.1 g, 8 %). The structure of *cis* Fmoc-APC was confirmed by single crystal X-ray analysis of its derivative. Fmoc-*cis*-APC, ^{1}H NMR(CD_3OD), 7.79 (d, 2H), 7.72 (d, 2H), 7.37 (t, 2), 7.24-7.32 (m, 4), 7.14-7.23 (m, 3), 4.37 (d, 2H), 4.24 (t, 1H), 2.55 (m, 1H), 2.28 (m, 2H), 1.84-1.96 (m, 2H) and 1.64-1.73 (m, 4H).

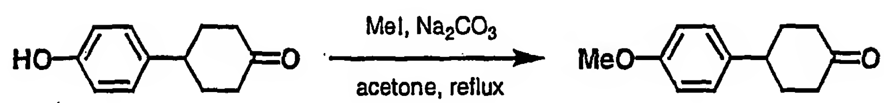
EXAMPLE 2

Preparation of

Fmoc-1-amino-4-(4-methoxyphenyl)cyclohexane-1-carboxylic acid

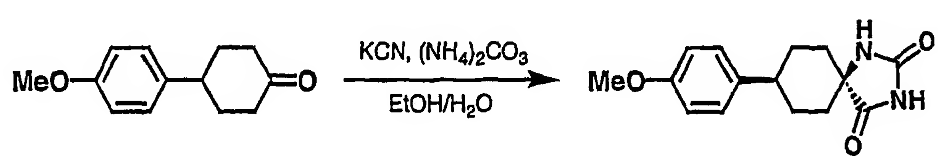
(Fmoc-4-MeOApc-OH)

Step 1:



A solution of 4-(4-hydroxyphenyl)cyclohexanone (5.0 g, 26.3 mmol) in acetone (100 mL) was treated with K_2CO_3 (14.5 g, 105 mmol, 4 equiv) and iodomethane (4.9 mL, 11.2 g, 78.6 mmol, 3 equiv.). The reaction was heated at 65 °C overnight. After the solvent was removed, the residue was treated with H_2O and extracted with EtOAc. The organic extracts were combined and washed with brine, dried over Na_2SO_4 and concentrated in vacuum to give the spectroscopically pure 4-(4-methoxyphenyl)cyclohexanone (5.34 g, 100 %). ^1H NMR($CDCl_3$) 7.16 (dt, 2H), 6.87 (dt, 2H), 3.78 (s, 3H), 2.99 (tt, 1H), 2.47-2.53 (m, 4H), 2.20 (m, 2H) and 1.83-1.98 (m, 2H); MS (electrospray) *m/e*, 205 $(M+1)^+$, Calcd for $C_{13}H_{16}O_2$, 204.

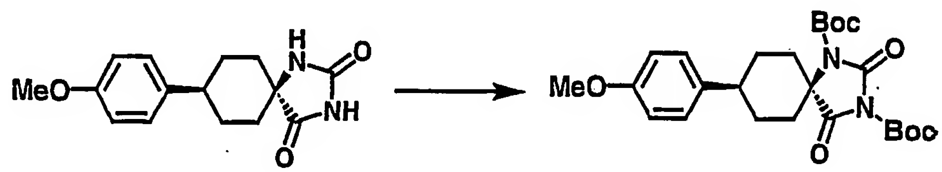
Step 2:



To a solution of the ketone (3.86 g, 18.9 mmol) in ethanol (50 mL) and water (15 mL) in a glass pressure bottle, were added ammonium carbonate (14.5 g, 151 mmol, 8 equiv.) and potassium cyanide (2.0 g, 30.7 mmol, 1.6 equiv.). The mixture was heated at 80-90 °C for 24 hrs. The cooled reaction mixture was added to icy water (300 ml) and stirred vigorously for

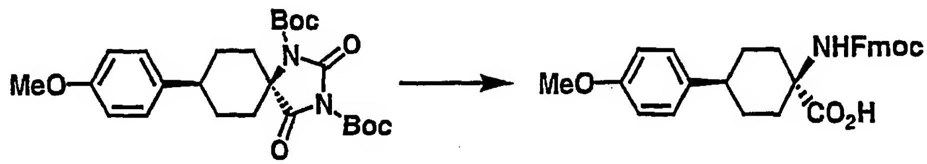
30 min. The resulting precipitate was suction filtered, washed thoroughly with water and dried to yield the hydantoin as a white solid (4.75 g, 91% yield). MS (electrospray) *m/e* 273 (M-H), Calcd for $C_{15}H_{18}N_2O_3$, 274.

Step 3:



To a suspension of the hydantoin (18.7 g, 68.25 mmol) in dry THF (450 mL) were added di-*tert*-butyl dicarbonate (37.2 g, 170.5 mmol, 2.5 equiv), triethylamine (10.5 mL, 7.59 g, 75.0 mmol, 1.1 equiv) and DMAP (460 mg, 3.65 mmol) in succession. About 15 minutes after the addition, the reaction turned into a clear yellow solution and was stirred overnight at room temperature. The reaction mixture was concentrated under reduced pressure to yield a solid that was then taken up in EtOAc (800 mL), washed with 1N HCl (3x50 mL), saturated aqueous Na_2CO_3 (2x50 mL) and brine (2x50 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude light yellow product was purified through flash chromatography (hexane/EtOAc, 90/10→70/30) to give the pure bis-Boc hydantoin as a white solid (27.6 g, 87%). ^{1}H NMR ($CDCl_3$): 7.28 (dt, 2H), 6.88 (dt, 2H), 3.79 (s, 3H), 2.14-2.24 (m, 2H), 1.59 (s, 9H) and 1.38 (s, 9H); MS (electrospray) *m/e* 538 $(M+MeCN+Na)^+$, Calcd for $C_{25}H_{34}N_2O_7$, 474.

Step 4:



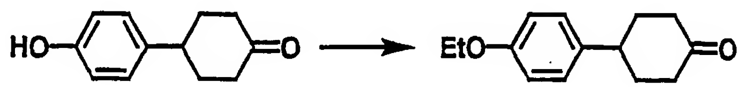
The bis-Boc hydantoin (15.08 g, 31.78 mmol) was dissolved in DME (500 mL) to give a clear solution. To this solution was added 1N NaOH (290 mL, 290 mmol) and the reaction was stirred overnight at room temperature, giving a slightly cloudy mixture. HPLC showed completion of the reaction. The reaction mixture was concentrated under reduced pressure to remove DME and extracted with Et_2O. Without purification, the resulting aqueous layer containing 1-amino-4-(4-methoxyphenyl)cyclohexane carboxylic acid (4-MeOAPC) was treated with 6N HCl to adjust the pH to 11-12. To this solution (~300 mL) were added DME (300 mL) and a solution of Fmoc-OSu (16.7 g, 49.42 mmol) in DME (200 mL) and the reaction was stirred overnight at room temperature. The reaction mixture was concentrated under reduced pressure to remove DME, acidified with 3N HCl, extracted with EtOAc. The combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4 and concentrated. The crude product was purified through flash chromatography (CH_2Cl_2/MeOH, 98/2→90/10) to give the pure product Fmoc-4-MeOAPC as a white solid (12.4 g, 83 % yield from the bis-Boc hydantoin). ^{1}H NMR (DMSO-d_6), 7.88 (d, 2H), 7.76 (d, 2H), 7.40 (t, 2H), 7.30 (t, 2H), 7.11 (d, 2H), 6.85 (d, 2H), 3.71 (s, 3H); MS (electrospray) *m/e* 470 (M-H), Calcd for $C_{29}H_{29}NO_5$, 471.

EXAMPLE 3

Preparation of

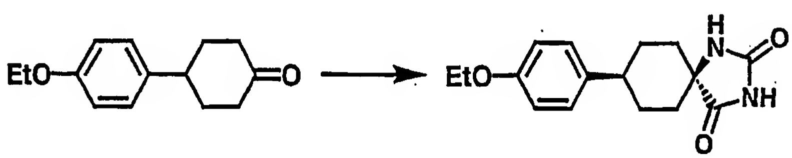
Fmoc-1-amino-4-(4-ethoxyphenyl)cyclohexane-1-carboxylic acid (**Fmoc-4-EtOApc-OH**)

Step 1:



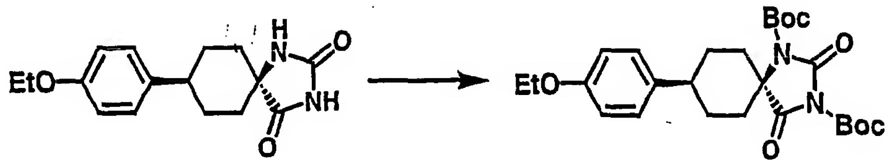
A solution of 4-(4-hydroxyphenyl)cyclohexanone (5.0 g, 26.3 mmol) in acetone (100 mL) was treated with K_2CO_3 (14.5 g, 105 mmol, 4 equiv) and iodoethane (10.5 mL, 20.5 g, 131 mmol, 5 equiv.). The reaction was heated at 65 °C overnight. After the solvent was removed, the residue was treated with H_2O and extracted with EtOAc. The organic extracts were combined and washed with brine, dried over Na_2SO_4 and concentrated in vacuum to give the spectroscopically pure 4-(4-ethoxyphenyl)cyclohexanone (5.74 g, 100 %). ^1H NMR ($CDCl_3$) 7.15 (dt, 2H), 6.86 (dt, 2H), 4.02 (q, 2H), 2.99 (tt, 1H), 2.46-2.54 (m, 4H), 2.16-2.24 (m, 2H), 1.83-2.00 (m, 2H) and 1.41 (t, 3H); MS (electrospray) *m/e*, 219 $(M+1)^+$, Calcd for $C_{14}H_{18}O_2$, 218.

Step 2:



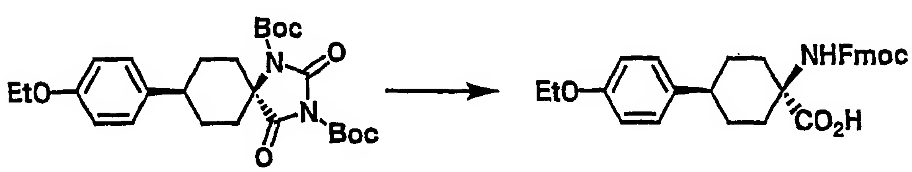
To a solution of the ketone (4.15 g, 19.01 mmol) in ethanol (50 mL) and water (15 mL) in a glass pressure bottle, were added ammonium carbonate (14.5 g, 151 mmol, 8 equiv.) and potassium cyanide (2.05 g, 31.42 mmol, 1.6 equiv.). The mixture was heated at 80-90 ^{0}C for 19 hrs. The cooled reaction mixture was added to icy water (300 ml) and stirred vigorously for 30 min. The resulting precipitate was suction filtered, washed thoroughly with water and dried to yield the hydantoin as a white solid (5.17 g, 94% yield). MS (electrospray) *m/e* 287 (M-H), Calcd for $C_{16}H_{20}N_2O_3$, 288.

Step 3:



To a suspension of the hydantoin (4.22 g, 14.65 mmol) in dry THF (100 mL) were added di-*tert*-butyl dicarbonate (7.98 g, 36.60 mmol, 2.5 equiv), triethylamine (2.3 mL, 1.63 g, 16.11 mmol, 1.1 equiv) and DMAP (89.4 mg, 0.73 mmol) in succession. About 15 minutes after the addition, the reaction turned into a clear yellow solution and was stirred overnight at room temperature. The reaction mixture was concentrated under reduced pressure to yield a solid that was then taken up in EtOAc (300 mL), washed with 1N HCl (3x20 mL), saturated aqueous Na2CO3 (2x20 mL) and brine (2x20 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude light yellow product was purified through flash chromatography (hexane/EtOAc, 90/10→70/30) to give the pure bis-Boc hydantoin as a white solid (7.01 g, 98%). ^{1}H NMR ($CDCl_3$): 7.27 (dt, 2H), 6.87 (dt, 2H), 4.02 (q, 2H), 1.59 (s, 9H), 1.43 (t, 3H) and 1.38 (s, 9H); MS (electrospray) *m/e* 999 $(2M+Na)^+$, Calcd for $C_{26}H_{36}N_2O_7$, 488.

Step 4:



The bis-Boc hydantoin (6.58 g, 13.46 mmol) was dissolved in DME (200 mL) to give a clear solution. To this solution was added 1N NaOH (121 mL, 121 mmol) and the reaction was stirred overnight at room temperature, giving a slightly cloudy mixture. HPLC showed completion of the reaction. The reaction mixture was concentrated under reduced pressure to

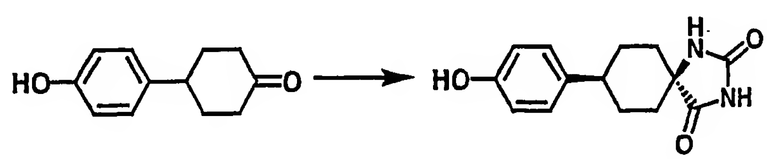
remove DME and extracted with Et_2O. Without purification, the resulting aqueous layer containing 1-amino-4-(4-ethoxyphenyl)cyclohexane carboxylic acid (4-EtOAPC) was treated with 6N HCl to adjust the pH to 11-12. To this solution (~130 mL) were added DME (100 mL) and a solution of Fmoc-OSu (6.83 g, 20.24 mmol) in DME (30 mL) and the reaction was stirred overnight at room temperature. The reaction mixture was concentrated under reduced pressure to remove DME, acidified with 3N HCl, extracted with EtOAc. The combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4 and concentrated. The crude product was purified through flash chromatography (CH_2Cl_2/MeOH, 98/2→90/10) to give the pure product as a white solid (5.56g, 85 % yield from the bis-Boc hydantoin). ^{1}H NMR (DMSO-d_6), 7.88 (d, 2H), 7.74 (d, 2H), 7.40 (td, 2H), 7.30 (td, 2H), 7.11 (d, 2H), 6.84 (d, 2H), 3.97 (q, 2H) and 1.29 (t, 3H); MS (electrospray) *m/e* 484 (M-H), Calcd for $C_{30}H_{31}NO_5$, 485.

EXAMPLE 4

Preparation of

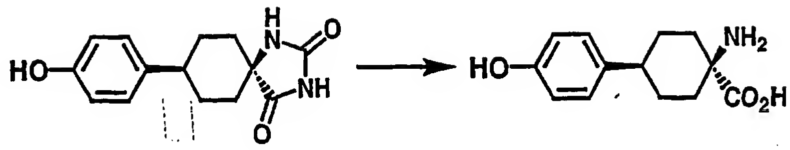
Fmoc-1-amino-4-(4-hydroxyphenyl)cyclohexane-1-carboxylic acid (**Fmoc-4-HOApc-OH**)

Step 1:



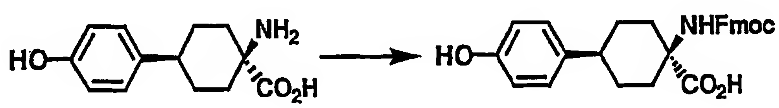
To a solution of 4-(4-hydroxyphenyl)cyclohexanone (2.00 g, 10.52 mmol) in ethanol (30 mL) and water (10 mL) in a glass pressure bottle, were added ammonium carbonate (6.17 g, 64.2 mmol, 6 equiv.) and potassium cyanide (1.07 g, 15.8 mmol, 1.5 equiv.). The mixture was heated at 80-90 ^{0}C overnight. The cooled reaction mixture was added to icy water (200 ml) and stirred vigorously for 30 min. The resulting precipitate was suction filtered, washed thoroughly with water and dried to yield the hydantoin as a white solid (2.56 g, 94% yield). MS (electrospray) *m/e* 261 $(M+H)^+$, Calcd for $C_{14}H_{16}N_2O_3$, 260.

Step 2:



The hydantoin (2.10 g, 8.06 mmol) was suspended in aqueous NaOH (6N, 100 mL) and heated at 130 °C for 2-3 days. Upon the completion of the hydrolysis, the reaction mixture was neutralized with conc. HCl to slightly acidic (pH~6). The resulting slurry was filtered, washed with water and dried to give 1-amino-4-(4-hydroxyphenyl)cyclohexane carboxylic acid (4-HOAPC) as a white solid (3.1 g, >100 % yield. contaminated with inorganic salt). MS (electrospray) *m/e* 236 $(M+H)^+$, Calcd for $C_{13}H_{17}NO_3$, 235.

Step 3:



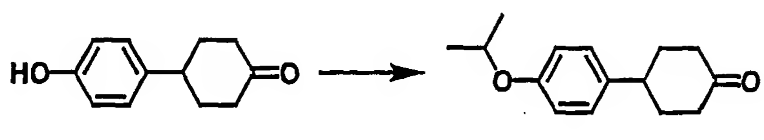
The crude APC from the last step (3.1 g) was treated with Fmoc-Cl (2.6g, 1.25 equiv) in dioxane (100 mL) and aqueous 10 % Na_2CO_3 (50 ml) and stirred vigorously overnight. The reaction mixture was concentrated to remove dioxane, neutralized with 6N HCl to slightly acidic (pH 5-6) and extracted with EtOAc. The combined organic extracts were washed with brine and dried over Na_2SO_4. Removal of the solvent gave the crude product which was purified on flash chromatography (hexane/EtOAc to CH_2Cl_2/MeOH) to give pure Fmoc-4-HOAPC (2.76 g, 75% overall yield for two steps). ^1H NMR(CD_3OD), 7.78 (d, 2H), 7.72 (d, 2H), 7.38 (t, 2H), 7.30 (td, 2H), 7.04 (d, 2H), 6.72 (dt, 2H), 4.38 (d, 2H), 4.25 (t, 1H), 2.46 (m, 1H), 2.24-2.34 (m, 2H) and 1.81-1.92 (m, 6H); MS (electrospray) *m/e* 456 (M-H), Calcd for $C_{28}H_{27}NO_5$, 457.

EXAMPLE 5

Preparation of

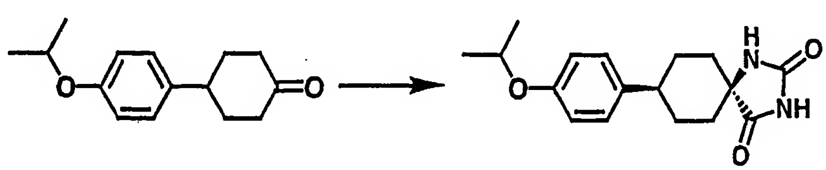
Fmoc-1-amino-4-(4-isopropoxyphenyl)cyclohexane-1-carboxylic acid (**Fmoc-4-iPrOApc-OH**)

Step 1:



A solution of 4-(4-hydroxyphenyl)cyclohexanone (6.0 g, 31.6 mmol) in DMF (90 mL) was treated with K_2CO_3 (21 g, 158 mmol, 5 equiv) and 2-iodopropane (15 mL, 26.8 g, 158 mmol, 5 equiv.). The reaction was heated at 100 °C overnight. After the solvent was removed, the residue was treated with H_2O and extracted with EtOAc. The organic extracts were combined and washed with brine, dried over Na_2SO_4 and concentrated in vacuum to give the spectroscopically pure 4-(4-isopropoxyphenyl)cyclohexanone (7.02 g, 95 %). ^{1}H NMR ($CDCl_3$): 7.14 (dt, 2H), 6.84 (dt, 2H), 4.3 (septet, 1H), 2.97 (tt, 1H), 2.46-2.52 (m, 4H), 2.16-2.24 (m, 2H), 1.83-1.98 (m, 2H) and 1.33 (d, 6H).

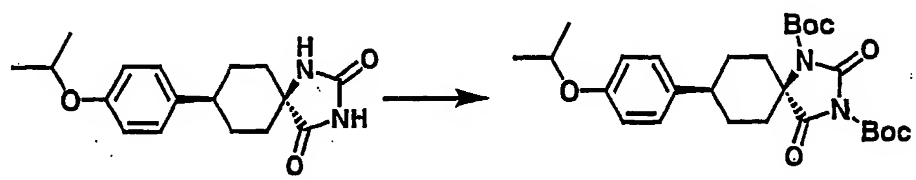
Step 2:



To a solution of the ketone (5.1 g, 21.98 mmol) in ethanol (90 mL) and water (30 mL) in a glass pressure bottle, were added ammonium carbonate (12.6 g; 131 mmol, 6 equiv.) and potassium cyanide (2.14 g, 32.9 mmol, 1.5 equiv.). The mixture was heated at 80-90 °C for 24 hrs. The cooled reaction mixture was added to icy water (400 ml) and stirred vigorously for 30 min. The resulting precipitate was suction filtered, washed thoroughly with water and

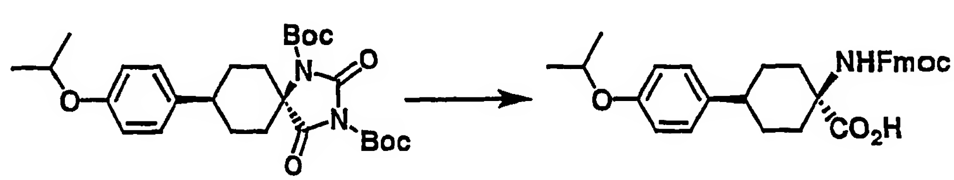
dried to yield hydantoin as a white solid (6.60 g, 99% yield). ^{1}H NMR (DMSO-d$_6$): 10.60 (s, 1H), 8.65 (s, 1H), 7.18 (d, 2H), 6.80 (d, 2H), 4.52 (septet, 1H), 2.43 (m, 1H), 1.85-2.15 (m, 2H), 1.56-1.80 (m, 6H) and 1.22 (d, 6H); MS (electrospray) *m/e* 301 (M-H), Calcd for $C_{17}H_{22}N_2O_3$, 302.

Step 3:



To a suspension of the hydantoin (5.8 g, 19.20 mmol) in dry THF (180 mL) were added di-*tert*-butyl dicarbonate (10.46 g, 48.0 mmol, 2.5 equiv), triethylamine (2.9 mL, 2.13 g, 21.12 mmol, 1.1 equiv) and DMAP (140 mg, 1.15 mmol) in succession. About 15 minutes after the addition, the reaction turned into a clear yellow solution and was stirred overnight at room temperature. The reaction mixture was concentrated under reduced pressure to yield a solid that was then taken up in EtOAc (600 mL), washed with 1N HCl (3x40 mL), saturated aqueous Na_2CO_3 (2x40 mL) and brine (2x40 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude light yellow product was purified through flash chromatography (hexane/EtOAc, 90/10→80/20) to give the pure bis-Boc hydantoin as a white solid (9.4 g, 98%). ^{1}H NMR ($CDCl_3$): 7.27 (dt, 2H), 6.87 (dt, 2H), 4.02 (q, 2H), 2.98 (t, 1H), 2.26-2.56 (m, 4H), 2.14-2.24 (m, 2H), 1.76-1.86 (m, 2H), 1.59 (s, 9H), 1.43 (t, 3H) and 1.38 (s, 9H); MS (electrospray) *m/e* 999 $(2M+Na)^+$, Calcd for $C_{26}H_{36}N_2O_7$, 488.

Step 4:



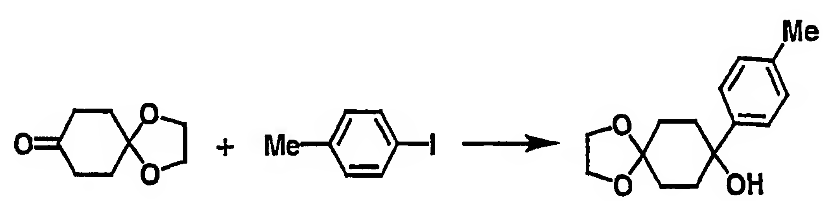
The bis-Boc hydantoin (4.34 g, 8.64 mmol) was dissolved in DME (100 mL) to give a clear solution. To this solution was added 1N NaOH (78 mL, 78 mmol) and the reaction was stirred overnight at room temperature, giving a fairly clear mixture. HPLC showed completion of the reaction. The reaction mixture was concentrated under reduced pressure to remove DME and extracted with Et_2O. Without purification, the resulting aqueous layer containing 1-amino-4-(4-isopropoxyphenyl)cyclohexane carboxylic acid (4-iPrOAPC) was treated with 6N HCl to adjust the pH to 11-12. To this solution (~90 mL) were added DME (120 mL) and a solution of Fmoc-OSu (3.49 g, 10.34 mmol, 1.2 equiv) in DME (20 mL) and the reaction was stirred overnight at room temperature. The reaction mixture was concentrated under reduced pressure to remove DME, acidified with 3N HCl, extracted with EtOAc. The combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4 and concentrated. The crude product was purified through flash chromatography (hexane/EtOAc→CH_2Cl_2/MeOH) to give the pure product as a white solid (3.23, 75 % yield from bis-Boc hydantoin). ^{1}H NMR(DMSO-d_6), 7.76 (d, 2H), 7.60 (d, 2H), 7.39 (t, 2H), 7.31 (t, 2H), 7.08 (d, 2H), 6.84 (d, 2H), 4.24 (m, 1H) and 1.34 (d, 6H); MS (electrospray) *m/e* 498 (M-H), Calcd for $C_{31}H_{33}NO_5$, 499.

EXAMPLE 6

Preparation of

Fmoc-1-amino-4-(4-methylphenyl)cyclohexane-1-carboxylic acid **(Fmoc-4-MeApc-OH)**

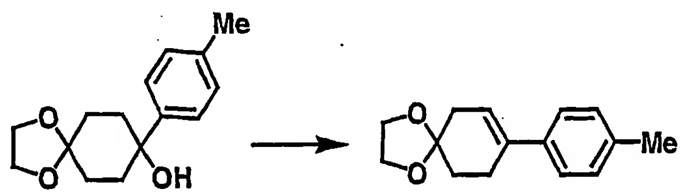
Step 1:



To a solution of 4-iodotoluene (10.9 g, 50.0 mmol) in dry THF (180 mL) at -78 ^{0}C was added a solution of n-BuLi (1.6 M, 31.0 mL, 50 mmol) in hexane over 20 min. The reaction was stirred for another 20 min before a solution of 1,4-cycloh¯xanedione *mono*-ethylene ketal

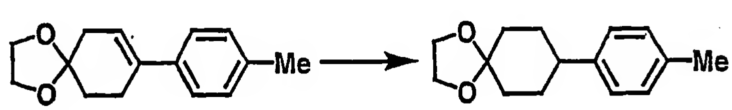
(6.0 g, 38.46 mmol) in dry THF (100 mL) was added dropwise. After stirred for 2 h at -78 ^{0}C, the reaction was quenched with aqueous NH_4Cl and extracted with EtOAc. The combined organic extracts were washed with brine, dried over Na_2SO_4, concentrated in vacuo to give the spectroscopically pure product as a white solid (9.34 g, 98% yield). ^{1}H NMR ($CDCl_3$): 7.41 (m, 2H), 7.16 (d, 2H), 3.98 (m, 4H), 2.34 (s, 3H); MS (EI) *m/e* 248 (M^+), Calcd for $C_{15}H_{20}O_3$, 248.

Step 2:



To a solution of the alcohol (9.10g, 36.65 mmol) in dry benzene (200 mL) in a flask equipped with a Dean-Stark trap, was added p-toluenesulfonic acid monohydrate (650 mg) and the reaction was heated at 100 °C for 3 hrs. The reaction was cooled to rt, diluted with EtOAc (500 mL) and washed with aqueous Na_2CO_3 (50 mL), brine (3x50 mL), dried over Na_2SO_4 and concentrated under reduced pressure to give the spectroscopically pure product (8.36 g, 100 yield), which was used for next step without purification. MS (EI) *m/e* 230 (M^+), 190 (M-OCH_2CH_2O), Calcd for $C_{15}H_{18}O_2$, 230.

Step 3:



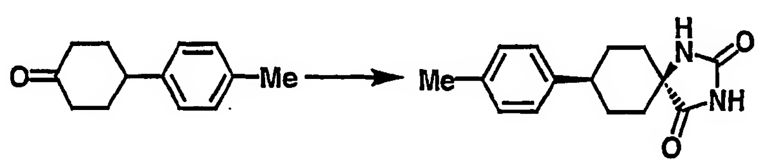
To a solution of the olefin (7.49 g) in EtOAc (180 mL) was added Pd/C (5 wt % on carbon, 800 mg) and the reaction was run under 40 psi of hydrogen for 3 hrs at room temperature. The catalyst was filtered off and the filtrate was concentrated to give the spectroscopically

pure product as a colorless oil (7.40 g, 100% yield). MS (EI) *m/e* 232 (M^+), 188 (M-OCH_2CH_2), Calcd for $C_{15}H_{20}O_2$, 232.

Step 4:

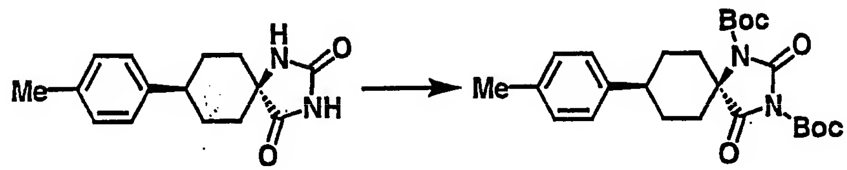
A solution of the ketal (6.90 g) in acetone (140 mL) was treated with 4N HCl (60 mL) and heated at 65 °C for 4 hrs. Solvent was removed and the residue was diluted with EtOAc and neutralized with 4N HCl. The aqueous was extracted with EtOAc. The combined organic extracts were washed with brine, dried and concentrated. The resulting crude product was used for next step without without purification (5.57 g, quantitative yield). MS (EI) *m/e* 188 (M^+), Calcd for $C_{13}H_{16}O$, 188.

Step 5:



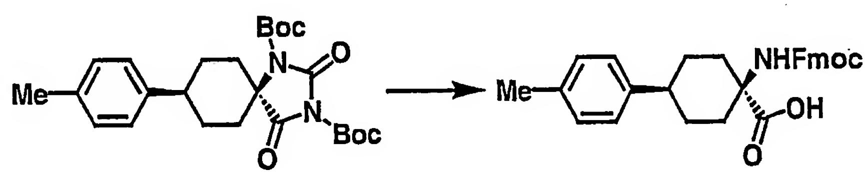
To a solution of 4-(4-methylphenyl)cyclohexanone (5.32 g, 28.3 mmol) in ethanol (90 mL) and water (30 mL) in a glass pressure bottle, were added ammonium carbonate (16.3 g, 169.8 mmol, 6 equiv.) and potassium cyanide (3.68 g, 56.5 mmol, 2 equiv.). The mixture was heated at 80-90 °C overnight. The cooled reaction mixture was added to icy water (400 ml) and stirred vigorously for 30 min. The resulting precipitate was suction filtered, washed thoroughly with water and dried to yield the hydantoin as a white solid (6.3 g, 86% yield). MS (electrospray) *m/e* 517 (2M+H), Calcd for $C_{15}H_{18}ClN_2O_2$, 258

Step 6:



To a suspension of the hydantoin (5.82 g, 22.55 mmol) in dry THF (250 mL) were added di-*tert*-butyl dicarbonate (12.3 g, 56.4 mmol, 2.5 equiv), triethylamine (3.5 mL, 2.5 g, 24.7 mmol, 1.1 equiv) and DMAP (275 mg, 2.25 mmol) in succession. The reaction turned into a clear yellow solution and was stirred overnight at room temperature. The reaction mixture was concentrated under reduced pressure to yield a solid that was then taken up in EtOAc (500 mL), washed with 1N HCl (3x50 mL), saturated aqueous Na_2CO_3 (2x50 mL) and brine (2x50 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude light yellow product was purified through flash chromatography (hexane/EtOAc, 90/10→70/30) to give the pure bis-Boc hydantoin as a white solid (10.03 g, 100% yield). ^1H NMR ($CDCl_3$): 7.26 (d, 2H), 6.87 (d, 2H), 3.00 (m, 1H), 2.32 (s, 3H), 1.59 (s, 9H) and 1.37 (s, 9H).

Step 7:



The bis-Boc hydantoin (6.40 g, 13.97 mmol) was dissolved in DME (200 mL) to give a clear solution. To this solution was added 1N NaOH (120 mL, 120 mmol) and the reaction was stirred overnight at room temperature, giving a slightly cloudy mixture. HPLC showed completion of the reaction. The reaction mixture was concentrated under reduced pressure to remove DME and extracted with Et_2O. Without purification, the resulting aqueous layer containing 1-amino-4-(4-methylphenyl)cyclohexane carboxylic acid (4-MeAPC) was treated

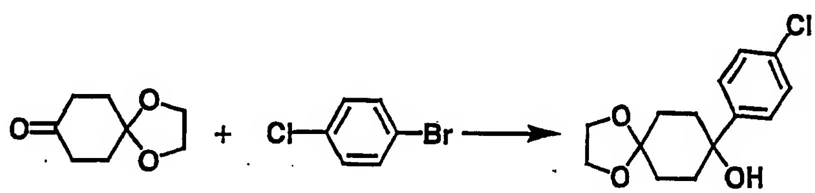
with 6N HCl to adjust the pH to 11-12. To this solution (~140 mL) were added DME (240 mL) and a solution of Fmoc-OSu (5.10 g, 15.13 mmol, 1.1 equiv) in DME (40 mL) and the reaction was stirred overnight at room temperature. The reaction mixture was concentrated under reduced pressure to remove DME, acidified with 3N HCl, extracted with EtOAc. The combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4 and concentrated. The crude product was purified through flash chromatography (CH_2Cl_2/MeOH, 98/2→90/10) to give the pure product as a white solid (4.35 g, 69 % yield from bis-Boc hydantoin). ^{1}H NMR (DMSO-d_6): 7.88 (d, 2H), 7.75 (d, 2H), 7.24-7.43 (m, 4H), 7.02-7.14 (m, 4H), 4.25 (m, 3H), 2.24 (s, 3H).

EXAMPLE 7

Preparation of

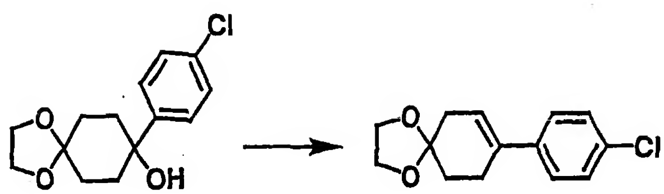
Fmoc-1-amino-4-(4-chlorophenyl)cyclohexane-1-carboxylic acid (**Fmoc-4-ClApc-OH**)

Step 1:



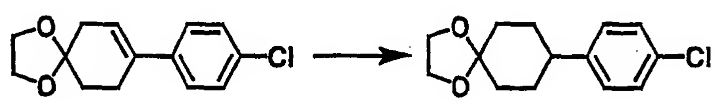
A solution of 4-chlorophenylbromide (7.5 g, 39.2 mmol) in dry THF (180 mL) was cooled to -78 ^{0}C and treated dropwise with a solution of n-BuLi (1.6 M, 25 mL, 40 mmol) in hexane over 20 min. The reaction was stirred for a further 30 min before a solution of 1,4-cyclohexanedione *mono*-ethylene ketal (6.0 g, 38.46 mmol) in dry THF (100 mL) was added dropwise. After stirred for 1 hr at -78 ^{0}C, the reaction was quenched with aqueous NH_4Cl and extracted with EtOAc. The combined organic extracts were washed with brine, dried over Na_2SO_4, concentrated in vacuo to give the spectroscopically pure product as a white solid (9.40 g, 91% yield). ^{1}H NMR ($CDCl_3$): 7.45 (m 2H), 7.31 (m, 2H), 3.99 (m, 4H), 2.02-2.20 (m, 4H), 1.75-1.82 (m, 2H), 1.66-1.73 (m, 2H), 1.54 (s, 1H); MS (EI) *m/e* 268 (M^+), 251 (M-OH), 250 (M-H_2O), Calcd for $C_{14}H_{17}ClO_3$, 268.

Step 2:



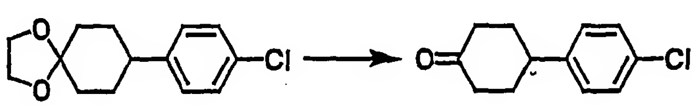
To a solution of the alcohol (6.78 g, 25.30 mmol) in dry benzene (120 mL) in a flask equipped with a Dean-Stark trap, was added p-toluenesulfonic acid monohydrate (960 mg) and the reaction was heated at reflux for 3 hrs. The reaction was cooled to rt, diluted with EtOAc (500 mL) and washed with aqueous Na_2CO_3 (50 mL), brine (3x50 mL), dried over Na_2SO_4 and concentrated under reduced pressure to give the spectroscopically pure product (6.30 g, 100 yield), which was used for next step without purification. MS (EI) *m/e* 250 (M^+), 190 (M-OCH_2CH_2O), Calcd for $C_{14}H_{15}ClO_2$, 250.

Step 3:



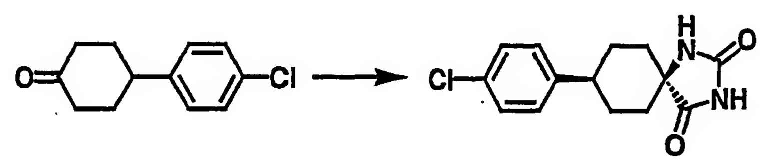
To a solution of the olefin (6.11 g) in EtOAc (120 mL) was added Pd/C (5 wt % on carbon, 600 mg) and the reaction was run under 5 psi of hydrogen for 3 hrs at room temperature. The catalyst was filtered off and the filtrate was concentrated to give the spectroscopically pure product as a colorless oil (6.10 g, 100% yield). MS (EI) *m/e* 252(M^+), Calcd for $C_{14}H_{17}ClO_2$, 252.

Step 4:



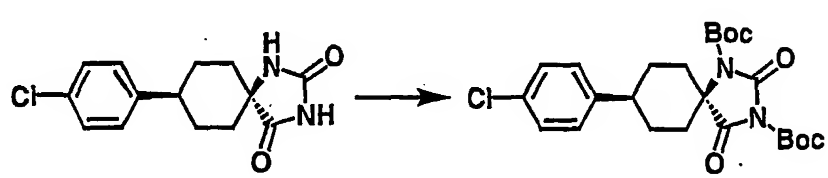
A solution of the ketal (5.81 g, 23.06 mmol) in acetone (200 mL) was treated with p-toluenesulfonic acid monohydrate (876 mg) and heated at 60 °C overnight. Solvent was removed and the residue was taken up in EtOAc, washed with aqueous Na_2CO_3 solution, brine, dried and concentrated to give the crude product as a yellow oil (5.38 g, >100% yield). Purification through flash chromatography (heaxane/EtOAc, 80/20→60/40) provided the ketone as a light yellow oil (4.54 g, 95% yield). MS (EI) *m/e* 208 (M^+), Calcd for $C_{12}H_{13}ClO_2$, 208.

Step 5:



To a solution of 4-(4-chlorophenyl)cyclohexanone (4.26 g, 20.48 mmol) in ethanol (90 mL) and water (30 mL) in a glass pressure bottle, were added ammonium carbonate (13.8 g, 144 mmol, 7 equiv) and potassium cyanide (3.56 g, 54.77 mmol, 2.5 equiv). The mixture was heated at 80-90 °C overnight. The cooled reaction mixture was added to icy water (400 ml) and stirred vigorously for 30 min. The resulting precipitate was suction filtered, washed thoroughly with water and dried to yield the hydantoin as a white solid (5.58 g, 98% yield). MS (electrospray) *m/e* 277 (M-H), Calcd for $C_{14}H_{15}ClN_2O_2$, 278

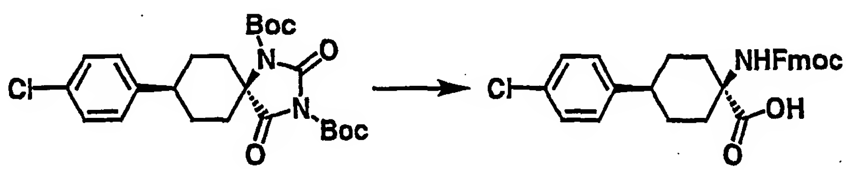
Step 6:



To a suspension of the hydantoin (5.15 g, 18.5 mmol) in dry THF (250 mL) were added di-*tert*-butyl dicarbonate (10.1 g, 46.3 mmol, 2.5 equiv), triethylamine (2.8 mL, 2.07 g, 20.45

mmol, 1.1 equiv) and DMAP (226 mg, 1.85 mmol) in succession. The reaction turned into a clear yellow solution and was stirred overnight at room temperature. The reaction mixture was concentrated under reduced pressure to yield a solid that was then taken up in EtOAc (500 mL), washed with 1N HCl (3x50 mL), saturated aqueous Na_2CO_3 (2x50 mL) and brine (2x50 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude light yellow product was purified through flash chromatography (hexane/EtOAc, 90/10→70/30) to give the pure bis-Boc hydantoin as a white solid (8.05 g, 91% yield). MS (electrospray) *m/e* 542 (M+Ma+MeCN), Calcd for $C_{24}H_{31}ClN_2O_6$, 478

Step 7:



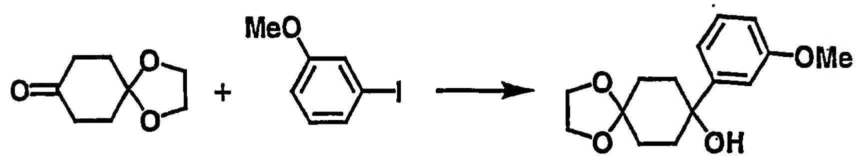
The bis-Boc hydantoin (6.41 g, 13.97 mmol) was dissolved in DME (200 mL) to give a clear solution. To this solution was added 1N NaOH (120 mL, 120 mmol) and the reaction was stirred overnight at room temperature, giving a slightly cloudy mixture. HPLC showed completion of the reaction. The reaction mixture was concentrated under reduced pressure to remove DME and extracted with Et_2O. Without purification, the resulting aqueous layer containing 1-amino-4-(4-chlorophenyl)cyclohexane carboxylic acid (4-ClAPC) was treated with 6N HCl to adjust the pH to 11-12. To this solution (~180 mL) were added DME (240 mL) and a solution of Fmoc-OSu (5.31 g, 15.74 mmol, 1.1 equiv) in DME (30 mL) and the reaction was stirred overnight at room temperature. The reaction mixture was concentrated under reduced pressure to remove DME, acidified with 3N HCl, extracted with EtOAc. The combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4 and concentrated. The crude product was purified through flash chromatography (CH_2Cl_2/MeOH, 98/2→90/10) to give the pure product as a white solid (5.04 g, 76% yield from the bis-Boc hydantoin). ^{1}H NMR (DMSO-d_6), 7.88 (d, 2H), 7.74 (d, 2H), 7.19-7.42 (m, 8H), 4.20-4.31 (m, 3H); MS (electrospray) *m/e* 474 (M-H), Calcd for $C_{28}H_{26}ClNO_4$, 475.

EXAMPLE 8

Preparation of

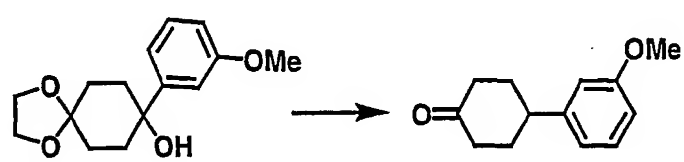
Fmoc-1-amino-4-(3-methoxyphenyl)cyclohexane-1-carboxylic acid (Fmoc-3-MeOApc-OH)

Step 1:



To a solution of 3-iodoanisole (11.7, 50.0 mmol, 1.3 equiv) in dry THF (180 mL) at -78 ^{0}C was added a solution of n-BuLi (1.6 M, 31.0 mL, 50 mmol, 1.3 equiv) in hexane over 25 min. The reaction was stirred for another 30 min before a solution of 1,4-cyclohexanedione *mono*-ethylene ketal (6.0 g, 38.46 mmol) in dry THF (100 mL) was added dropwise. After stirred for 2 h at -78 ^{0}C, the reaction was quenched with aqueous NH_4Cl and extracted with EtOAc. The combined organic extracts were washed with brine, dried over Na_2SO_4, concentrated in vacuo to give the spectroscopically pure product as a white solid (9.34 g, 98% yield). ^{1}H NMR ($CDCl_3$): 7.26 (dd, 1H), 7.06-7.11 (m, 2H), 6.79 (dd, 1H), 3.98 (m, 4H), 3.81 (s, 3H).

Step 2:

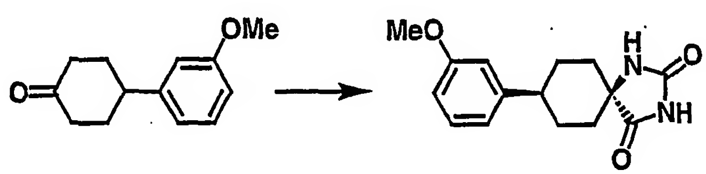


To a stirred solution of the alcohol (5.6 g, 21.21 mmol) in dry CH_2Cl_2 (200 mL) under a nitrogen atmosphere at salt-ice bath temperature, were added in succession triethylsilane (10.2 mL,7.4 g, 63.63 mmol, 3 equiv) and boron trifluoride etherate (21.5 mL, 24.1 g, 169.7 mmol, 8 equiv). The reaction mixture was then allowed to warm to room temperature and

stirred for 3 hrs before washed with 10% aqueous K_2CO_3 solution and H_2O, dried over Na_2SO_4, and concentrated in vacuo to give the deoxygenation compound as an oil (4.91g), which was sufficiently pure for direct use.

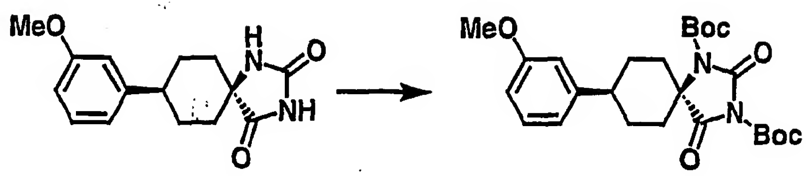
This crude intermediate was dissolved in acetone (130 mL) and treated with 4N HCl (60 mL) and heated at 65 °C for 4 hrs. Solvent was removed under reduced pressure and the residue was diluted with EtOAc and neutralized with 4N NaOH solution. The aqueous layer was extracted with EtOAc and the combined organic extracts were washed with brine, dried and concentrated. The resulting residue was purified by flash chromatography on silica gel (80/20→60/40) to give the ketone (3.67 g, 85% overall yield) as a yellow oil. ^{1}H NMR ($CDCl_3$): 7.25 (dt, 1H), 6.75-6.86 (m, 3H), 3.81 (s, 3H), 3.00 (tt, 1H); MS (EI) *m/e* 204 (M+), Calcd for $C_{13}H_{16}O_2$, 204.

Step 3:



To a solution of 4-(3-methoxyphenyl)cyclohexanone (3.10 g, 15.20 mmol) in ethanol (60 mL) and water (20 mL) in a glass pressure bottle, were added ammonium carbonate (8.75 g, 91.20 mmol, 6 equiv.) and potassium cyanide (1.98 g, 30.40 mmol, 2 equiv.). The mixture was heated at 80-90 °C overnight. The cooled reaction mixture was added to icy water (300 ml) and stirred vigorously for 30 min. The resulting precipitate was suction filtered, washed thoroughly with water and dried to yield the hydantoin as a white solid (4.08 g, 98% yield). ^{1}H NMR (DMSO-d_6): 7.11 (d, 1H), 6.70-6.94 (m, 3H), 3.72 (s, 3H); MS (electrospray) *m/e* 316 (M+MeCN+H), Calcd for $C_{15}H_{18}N_2O_3$, 274.

Step 4:



To a suspension of the hydantoin (5.29 g, 19.30 mmol) in dry THF (250 mL) were added di-*tert*-butyl dicarbonate (10.5 g, 48.16 mmol, 2.5 equiv), triethylamine (3.0 mL, 2.17 g, 21.52 mmol, 1.1 equiv) and DMAP (235 mg, 1.92 mmol) in succession. The reaction turned into a clear yellow solution and was stirred overnight at room temperature. The reaction mixture was concentrated under reduced pressure to yield a solid that was then taken up in EtOAc (500 mL), washed with 1N HCl (3x50 mL), saturated aqueous Na_2CO_3 (2x50 mL) and brine (2x50 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude light yellow product was purified through flash chromatography (hexane/EtOAc, 80/20→60/40) to give the pure bis-Boc hydantoin as a white solid (8.70 g, 95% yield). MS (electrospray) *m/e* 538 (M+MeCN+Na), Calcd for $C_{25}H_{34}N_2O_7$, 474.

Step 5:

The bis-Boc hydantoin (2.30 g, 4.84 mmol) was dissolved in DME (80 mL) to give a clear solution. To this solution was added 1N NaOH (44 mL, 44 mmol) and the reaction was stirred overnight at room temperature, giving a slightly cloudy mixture. HPLC showed completion of the reaction. The reaction mixture was concentrated under reduced pressure to remove DME and extracted with Et_2O. Without purification, the resulting aqueous layer containing 1-amino-4-(3-methoxyphenyl)cyclohexane carboxylic acid (3-MeOAPC) was treated with 6N HCl to adjust the pH to 11-12. To this solution (~40 mL) were added

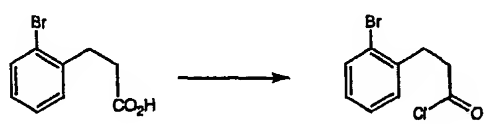
dioxane (80 mL) and Fmoc-Cl (1.73 g, 6.76 mmol, 1.4 equiv) and the reaction was stirred overnight at room temperature. The reaction mixture was then concentrated under reduced pressure to remove DME, neutralized with 3N HCl and extracted with EtOAc. The combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4 and concentrated. The crude product was purified by flash chromatography on silica gel (CH_2Cl_2/MeOH, 98/2→90/10) to give the pure product as a white solid (1.98 g, 87 % yield from bis-Boc hydantoin). ^{1}H NMR (DMSO-d_6), 7.88 (d, 2H), 7.75 (d, 2H), 7.40 (td, 2H), 7.30 (td, 2H), 7.21 (m, 1H), 6.71-6.80 (m, 3H), 3.72 (s, 3H); MS (electrospray) *m/e* 494 (M+Na), Calcd for $C_{29}H_{29}NO_5$, 471.

EXAMPLE 9

Preparation of

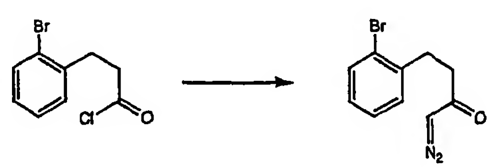
Fmoc-(D,L)-5-bromo-2 aminotetraline-2-carboxylic acid **(Fmoc-(D,L) 5-Br-Atc-OH)**

Step 1:



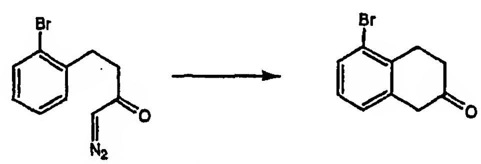
A mixture of 3-(2-bromophenyl)propanoic acid (prepared in 2 steps from 2-bromobenzyl bromide, 2.0 g, 8.73 mmole), oxalyl chloride (1.14 ml, 13.1 mmole) and methylene chloride (20 ml) was cooled in an ice bath and N,N-dimethylformamide (34 µL, 0.44 mmole) was added dropwise. The mixture was stirred at room temperature for 3 hours. Concentration in vacuo gave 3-(2-bromophenyl)propanoyl chloride which was taken up in methylene chloride and used in the next step as a crude.

Step 2:



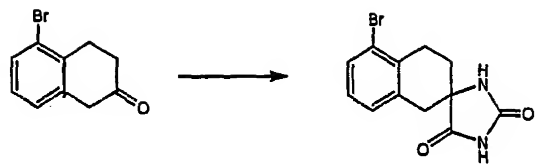
A solution of the above acid chloride (crude, 8.73 mmole) in methylene chloride was slowly added to a solution of diazomethane (generated from 5.70 g of 1-methyl-3-nitro-1-nitrosoguanidine) in ether (40 ml) cooled in an ice bath. The mixture was then warmed up to room temperature and stirred overnight. The mixture was concentrated in vacuo and purified by column chromatography (10 → 20% ethyl acetate/hexanes) to give 1-diazo-4-(2-bromophenyl)butan-2-one (1.88 g, 85% over 2 steps). ^{1}H NMR ($CDCl_3$) δ 7.50 (1H, d, phenyl), 7.24 (2H, m, phenyl), 7.06 (1H, m, phenyl), 5.21 (1H, broad s, diazo), 3.05 (2H, t, benzylic), 2.62 (2H, m).

Step 3:



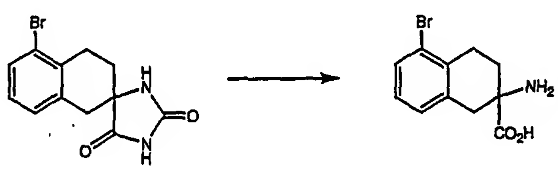
To a mixture of rhodium (II) acetate dimer (15 mg, 0.068 mmole) in methylene chloride (120 ml) under reflux was slowly added a solution of 1-diazo-4-(2-bromophenyl)butan-2-one (1.74 g, 6.85 mmole) in methylene chloride (30 ml). After the addition was complete, the mixture was refluxed for an extra twenty minutes. The mixture was cooled to room temperature, trifluoroacetic acid (1.5 ml) was added and the mixture was stirred at room temperature for an hour. The reaction was quenched with saturated sodium bicarbonate solution. The layers were separated and the methylene chloride layer was washed once more with saturated sodium bicarbonate solution. The combined aqueous layers were back-extracted with methylene chloride. The combined organic layers were dried over magnesium sulfate, filtered and concentrated in vacuo to give a brown oil. Purification by column chromatography (10 → 15% ethyl acetate/hexanes) gave 5-bromo-β-tetralone (1.18 g, 77% yield) as a colorless oil. ^{1}H NMR ($CDCl_3$) δ 7.46 (1H, t, phenyl), 7.05-7.09 (2H, m, phenyl), 3.58 (2H, s, benzylic), 3.22 (2H, t, benzylic), 2.54 (2H, t).

Step 4:



A mixture of 5-bromo-β-tetralone (1.18 g, 5.24 mmole), potassium cyanide (512 mg, 7.86 mmole), ammonium carbonate (3.0 g, 31.22 mmole), ethanol (25 ml) and water (5 ml) in a sealed, thick walled pressure flask was heated in a 80°C oil bath for 4 days. After cooling to room temperature, the white slurry was poured into ice-water and stirred at room temperature for a couple of hours. Filtration followed by air-drying gave hydantoin (1.31 g, 85%). ^1H NMR (DMSO-d_6) δ 10.71 (1H, broad, NH), 8.28 (1H, broad s, NH), 7.0-7.5 (3H, m, phenyl). LRMS (Electrospray): $C_{12}H_{11}BrN_2O_2$, calc. 294; observed: 293 (M-H), 295 (M-H).

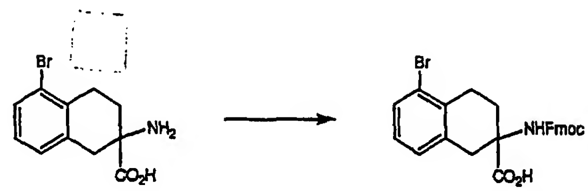
Step 5:



A mixture of hydantoin (1.287 g, 4.36 mmole), $Ba(OH)_2$. H_2O (4.20 g, 22.2 mmole) in water (25 ml) in a sealed, thick walled pressure flask was heated in a 125°C oil bath for 4 days. The reaction mixture was cooled to room temperature, acidified to ~ pH 3 using 4N sulfuric acid while being stirred vigorously. The suspension was stirred in a boiling water bath for one hour and cooled to room temperature. The white suspension was filtered and the precipitates rinsed with water. The combined filtrate and washings were concentrated in vacuo to ~ 20 ml. Neutralization with concentrated ammonium hydroxide solution gave white precipitate which were filtered, washed with water and dried in vacuo overnight to give racemic 5-bromo-2 aminotetraline-2-carboxylic acid (893 mg, 76% yield). LRMS

(Electrospray): $C_{11}H_{12}BrNO_2$, calc. 269; observed: 270 (M+H), 272 (M+H), 268 (M-H), 270 (M-H).

Step 6:



A mixture of racemic 5-bromo-2 aminotetraline-2-carboxylic acid (882 mg, 3.27 mmole), triethylamine (0.60 ml, 4.30 mmole), 9-fluorenylmethyl succinimidyl carbonate (Fmoc-OSu, 1.32 g, 3.91 mmole) in acetonitrile (30 ml) and water (30 ml) was stirred at room temperature overnight. TLC analysis of the reaction the next day indicated the presence of starting material amino acid. 9-fluorenylmethyl succinimidyl carbonate (0.25 g), triethylamine (0.6 ml) and acetonitrile (5 ml) was added and the mixture was stirred at room temperature for another day. The reaction mixture was concentrated in vacuo to remove most of the acetonitrile, acidified to pH ~3 with 10% aqueous citric acid solution, and the white emulsion extracted twice with methylene chloride. The combined organic layers were washed with water, brine, dried over magnesium sulfate. Filtration and concentration gave a crude oil which was purified by column chromatography (eluted with 2 → 5→ 10% methanol/methylene chloride) to give racemic Fmoc-5-bromo-2 aminotetraline-2-carboxylic acid (1.09 g, 68% yield) as a white solid. HRMS (FAB): $C_{26}H_{22}BrNNaO_4$ (M+Na) calc. 514.0630; observed: 514.0643.

EXAMPLE 10

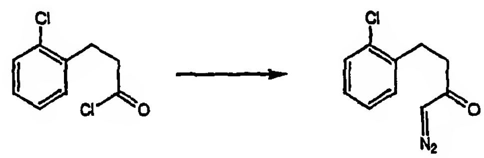
Preparation of

Fmoc-(D,L)-5-chloro-2 aminotetraline-2-carboxylic acid (**Fmoc-(D,L) 5-ClAtc-OH**)

Step 1:

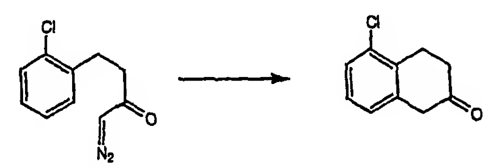
A mixture of 3-(2-chlorophenyl)propanoic acid (5.0 g, 27.1 mmole), thionyl chloride (10.9 ml, 149 mmole) and toluene (75 ml) was refluxed for two hours. Concentration in vacuo gave 3-(2-chlorophenyl)propanoyl chloride which was taken up in methylene chloride and used in the next step without further purification.

Step 2:



A solution of the above acid chloride (crude, 27.1 mmole) in methylene chloride was slowly added to a solution of diazomethane (generated from 17.8 g of 1-methyl-3-nitro-1-nitrosoguanidine) in ether (120 ml) cooled in an ice bath. The mixture was then warmed up to room temperature and stirred overnight. The mixture was concentrated in vacuo to give 1-diazo-4-(2-chlorophenyl)butan-2-one (5.87 g, > 100% over 2 steps) as a bright yellow oil. The compound was used in the next step without further purification. ^{1}H NMR ($CDCl_3$) δ 7.05-7.32 (4H, m, phenyl), 5.13 (1H, broad s, diazo), 3.00 (2H, t, benzylic), 2.57 (2H, m).

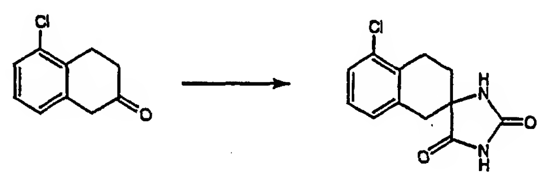
Step 3



To a mixture of rhodium (II) acetate dimer (60 mg, 0.27 mmole) in methylene chloride (400 ml) under reflux was slowly added a solution of crude 1-diazo-4-(2-bromophenyl)butan-2-one (5.87 g, 27.1 mmole theoretical) in methylene chloride (50 ml). After the addition was complete, the mixture was refluxed for an extra twenty minutes. The mixture was cooled to room temperature, trifluoroacetic acid (6.0 ml) was added and the mixture was stirred at

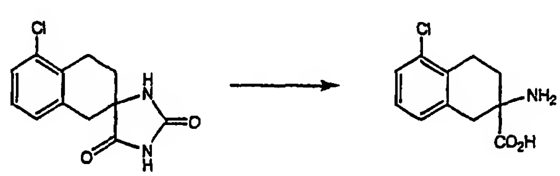
room temperature for two hours. The reaction was quenched with saturated sodium bicarbonate solution. The layers were separated and the methylene chloride layer was washed once more with saturated sodium bicarbonate solution. The combined aqueous layers were back-extracted with methylene chloride. The combined organic layers were dried over magnesium sulfate, filtered and concentrated in vacuo to give a brown oil. Purification by column chromatography (10 → 15% ethyl acetate/hexanes) gave 5-chloro-β-tetralone (3.32 g, 68% yield for steps a through c) as a light brown oil. ^{1}H NMR ($CDCl_3$) δ 7.30 (1H, m, phenyl), 7.15 (1H, t, phenyl), 7.05 (1H, d, phenyl), 3.60 (2H, s, benzylic), 3.22 (2H, t, benzylic), 2.56 (2H, t).

Step 4:



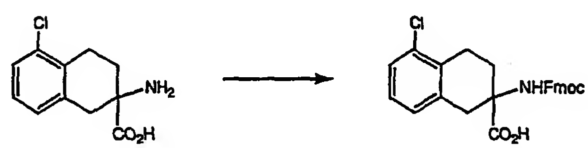
A mixture of 5-chloro-β-tetralone (880 mg, 4.87 mmole), potassium cyanide (500 mg, 7.67 mmole), ammonium carbonate (2.85 g, 29.7 mmole), ethanol (24 ml) and water (6 ml) in a sealed, thick-walled pressure flask was heated in a 80°C oil bath for 66 hours. After cooling to room temperature, the slurry was poured into ice-water and stirred at room temperature for a couple of hours. Filtration followed by air-drying gave hydantoin (0.92 g, 75%) as a light beige solid. ^{1}H NMR (DMSO-d_6) δ 10.70 (1H, broad, NH), 8.25 (1H, broad s, NH), 7.0-7.3 (3H, m, phenyl). LRMS (Electrospray): $C_{12}H_{11}ClN_2O_2$, calc. 250; observed: 249 (M-H), 251 (M-H).

Step 5:



A mixture of hydantoin (880 mg, 3.51 mmole), $Ba(OH)_2 \cdot H_2O$ (3.40 g, 18.0 mmole) in water (50 ml, too dilute) in a sealed, thick walled pressure flask was heated in a 125°C oil bath for 2 days. The reaction mixture was cooled to room temperature, acidified to ~ pH 3 using 4N sulfuric acid while being stirred vigorously. The suspension was stirred in a boiling water bath for two hours and cooled to room temperature. The white suspension was filtered and the precipitates rinsed with water. The combined filtrate and washings were concentrated in vacuo to ~ 50 ml. Neutralization with concentrated ammonium hydroxide solution gave white precipitate which were filtered, washed with water and dried in vacuo overnight to give racemic 5-chloro-2-aminotetraline-2-carboxylic acid (788 mg, 99% yield). LRMS (Electrospray): $C_{11}H_{12}ClNO_2$, calc. 225; observed: 226 (M+H), 228 (M+H), 224 (M-H), 226 (M-H).

Step 6:



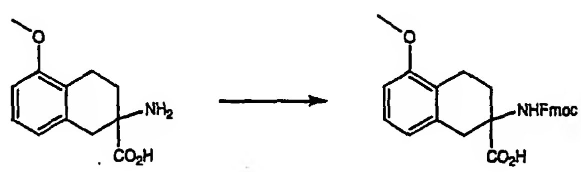
A mixture of racemic 5-chloro-2-aminotetraline-2-carboxylic acid (402 mg, 1.78 mmole), triethylamine (0:38 ml, 2.73 mmole), 9-fluorenylmethyl succinimidyl carbonate (Fmoc-OSu, 904 mg, 2.68 mmole) in acetonitrile (20 ml) and water (20 ml) was stirred at room temperature for two days. TLC analysis of the reaction after two days indicated the presence of starting material amino acid. 9-fluorenylmethyl succinimidyl carbonate (0.12 g) and triethylamine (0.1 ml) was added and the mixture was stirred at room temperature for another day. The reaction mixture was concentrated in vacuo to remove most of the acetonitrile, acidified to pH ~3 with 10% aqueous citric acid solution, and the white emulsion extracted three times with ethyl acetate. The combined organic layers were washed with water, brine, dried over magnesium sulfate. Filtration and concentration gave a crude oil which was purified by column chromatography (eluted with 3 → 6→ 8% methanol/methylene chloride) to give racemic Fmoc-5-chloro-2-aminotetraline-2-carboxylic acid (540 mg, 68% yield) as a white solid. HRMS (EI): $C_{26}H_{22}ClNO_4$ (M) calc. 447.1237; observed: 447.1234.

EXAMPLE 11

Preparation of

Fmoc-(D,L)-5-methoxy-2-aminotetraline-2-carboxylic acid **(Fmoc-(D,L) 5-MeOAtc-OH)**

Step 1:



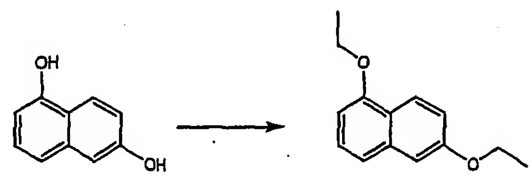
A mixture of racemic 5-methoxy-2-aminotetraline-2-carboxylic acid (prepared according to Obrecht, D. *et. al. Helv. Chim Acta.* **1992**, *75*, 1666) (802 mg, 3.62 mmole), triethylamine (0.62 ml, 4.45 mmole), 9-fluorenylmethyl succinimidyl carbonate (Fmoc-OSu, 1.47 g, 4.36 mmole) in acetonitrile (25 ml) and water (25 ml) was stirred at room temperature for 30 hours. TLC analysis of the reaction indicated the presence of starting material amino acid. 9-fluorenylmethyl succinimidyl carbonate (370 mg) and triethylamine (0.6 ml) were added and the mixture was stirred at room temperature for another 24 hours. The reaction mixture was concentrated in vacuo to remove most of the acetonitrile, acidified to pH ~3 with 10% aqueous citric acid solution, and the white emulsion was extracted three times with ethyl acetate. The combined organic layers were washed with water, brine and dried over magnesium sulfate. Filtration and concentration gave a crude oil which was purified by column chromatography (eluted with 1 → 3 → 5 → 10% methanol/methylene chloride) to give racemic Fmoc-5-methoxy-2-aminotetraline-2-carboxylic acid (1.14 g, 71% yield) as an off-white solid. HRMS (FAB): $C_{27}H_{26}NO_5$ (M+H) calc. 444.1812; observed: 444.1814.

EXAMPLE 12

Preparation of

Fmoc-(D,L)-5-ethoxy-2-aminotetraline-2-carboxylic acid (**Fmoc-(D,L) 5-EtOAtc-OH**)

Step 1:

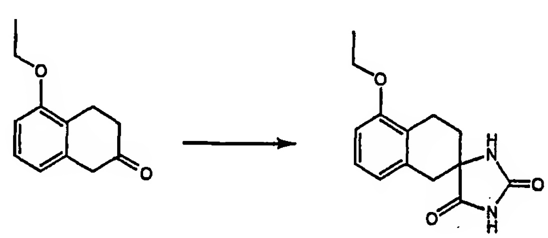


A mixture of 1,6-dihydroxynaphthalene (5.02 g, 31.3 mmole), anhydrous potassium carbonate (52.0 g, 376 mmole), N,N-dimethylformamide (50 ml) and iodoethane (15 ml, 188 mmole) was stirred in a 35°C oil bath for 24 hours. The reaction mixture was filtered and the solid residue was rinsed thoroughly with ethyl ether. The filtrate and the washings were combined and concentrated in vacuo to remove most of the solvents. The brown residue was partitioned between water and ether and the layers were separated. The ether layer was washed with water. The combined aqueous layers were back extracted with ether. The ether extracts were combined, washed with brine and dried over magnesium sulfate. Filtration and concentration gave a crude brown solid (6.74 g, 99% yield). Recrystallization of the crude product from hot methanol gave 1,6-diethoxynaphthalene (4.36 g, 64% yield, first crop) as a light brown solid. ^{1}H NMR ($CDCl_3$) δ 8.20 (1H, d, phenyl), 7.06-7.36 (4H, m, phenyl), 6.66 (1H, dd, phenyl), 4.10-4.23 (4H, 2 sets of q, 2 CH_2), 1.45-1.56 (6H, 2 sets of t, 2 CH_3).

Step 2:

To a refluxing solution of 1,6-diethoxynaphthalene (4.15 g, 19.2 mmole) in absolute ethanol (100 ml) was carefully added small pieces of sodium metal (6.8 g, 296 mmole) over 60 minutes. The mixture was refluxed for another 90 minutes. TLC indicated the presence of unreacted starting material. Extra sodium metal (1.0 g, 43.5 mmole) was added and the reaction mixture was refluxed for another 60 minutes. The reaction was cooled to room temperature, quenched with water and acidified with concentrated hydrochloric acid. The mixture was concentrated in vacuo to remove most of the ethanol. The aqueous mixture was extracted three times with ether. The combined organic layers were washed with water and dried over sodium sulfate. Filtration and concentration gave a brown solid which, was dissolved in 1:1 ethanol/water (200 ml), then *p*-toluenesulfonic acid (400 mg) was added. The mixture was refluxed for 210 minutes. Extra *p*-toluenesulfonic acid (100 mg) was added and the mixture was refluxed for another 60 minutes. After cooling to room temperature, most of the ethanol was removed under reduced pressure. The aqueous mixture was extracted three times with ether and the combined organic layers were washed with water, saturated sodium chloride solution and dried over sodium sulfate. Filtration and concentration gave a brwon oil which was purified by column chromatography (7% ethyl acetate/hexanes) to give 5-ethoxy-β-tetralone (2.43 g, 67% yield) as a light yellow oil. ^1H NMR ($CDCl_3$) δ 7.15 (1H, t, phenyl), 6.76 (1H, d, phenyl), 6.72 (1H, d, phenyl), 4.05 (2H, q, CH_2), 3.56 (2H, s, benzylic), 3.10 (2H, t, benzylic), 2.53 (2H, t), 1.44 (3H, t, CH_3).

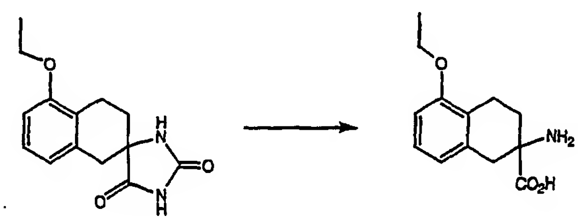
Step 3:



A mixture of 5-ethoxy-β-tetralone (2.23 g, 11.7 mmole), potassium cyanide (1.20 g, 18.4 mmole), ammonium carbonate (6.75 g, 70.2 mmole), ethanol (80 ml) and water (20 ml) in a sealed, thick walled pressure flask was heated in a 80°C oil bath for 3 days. After cooling to

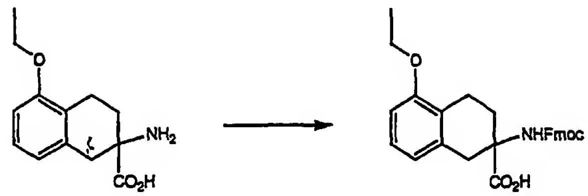
room temperature, the slurry was poured into ice-water and stirred at room temperature for a couple of hours. Filtration followed by air-drying gave hydantoin (2.69 g, 88%) as a beige solid. ^{1}H NMR (DMSO-d_6) δ 10.65 (1H, broad s, NH), 8.22 (1H, broad s, NH), 7.06 (1H, t, phenyl), 6.75 (1H, d, phenyl), 6.65 (1H, d, phenyl), 3.98 (2H, q, CH_2), 1.32 (3H, t, CH_3). LRMS (Electrospray): $C_{14}H_{16}N_2O_3$, calc. 259; observed: 258 (M-H).

Step 4:



A mixture of hydantoin (2.57 g, 9.87 mmole), $Ba(OH)_2$. H_2O (9.40 g, 49.6 mmole) in water (200 ml, too dilute) in a sealed, thick walled pressure flask was heated in a 105°C oil bath for 39 hours. Extra $Ba(OH)_2$. H_2O (9.40 g, 49.6 mmole) was added and the mixture was heated in a 125°C oil bath for an additional 21 hours. The reaction mixture was cooled to room temperature, acidified to ~ pH 3 using 4N sulfuric acid while being stirred vigorously. The suspension was stirred in a boiling water bath for one hour and cooled to room temperature. The white suspension was filtered and the precipitates rinsed with water. The combined filtrate and washings were concentrated in vacuo to ~ 75 ml. Neutralization with concentrated ammonium hydroxide solution gave white precipitate which were filtered, washed with water and air-dried to give racemic 5-ethoxy-2-aminotetraline-2-carboxylic acid (2.34 g, quantitative yield) as a light beige solid. LRMS (Electrospray): $C_{13}H_{17}NO_3$, calc. 235; observed: 236 (M+H), 234 (M-H).

Step 5:



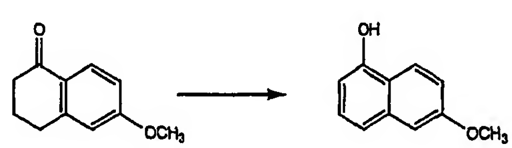
A mixture of racemic 5-ethoxy-2-aminotetraline-2-carboxylic acid (2.22 g, 9.44 mmole), triethylamine (2.00 ml, 14.3 mmole), 9-fluorenylmethyl succinimidyl carbonate (Fmoc-OSu, 4.81 g, 14.3 mmole) in acetonitrile (75 ml) and water (75 ml) was stirred at room temperature for two days. TLC analysis of the reaction indicated the presence of starting material amino acid. 9-fluorenylmethyl succinimidyl carbonate (645 mg) and triethylamine (1.0 ml) was added and the mixture was stirred at room temperature for another day. The reaction mixture was concentrated in vacuo to remove most of the acetonitrile, acidified to pH ~3 with 10% aqueous citric acid solution, and the white emulsion extracted three times with ethyl acetate. The combined organic layers were washed with water, brine, dried over magnesium sulfate. Filtration and concentration gave a crude oil which was purified by column chromatography (eluted with 3 → 5 → 10% methanol/methylene chloride) to give racemic Fmoc-5-ethoxy-2-aminotetraline-2-carboxylic acid (4.66 g, > quantitative yield) as a white solid. HRMS (FAB): $C_{28}H_{28}NO_5$ (M+H) calc. 458.1967; observed: 458.1985.

EXAMPLE 13

Preparation of

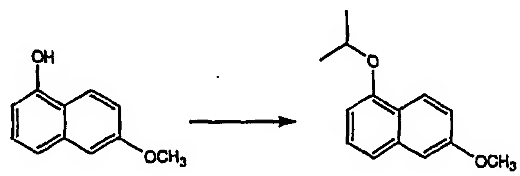
Fmoc-(D,L)-5-isopropoxy-2-aminotetraline-2-carboxylic acid (**Fmoc-(D,L) 5-iPrOAtc-OH**)

Step 1:



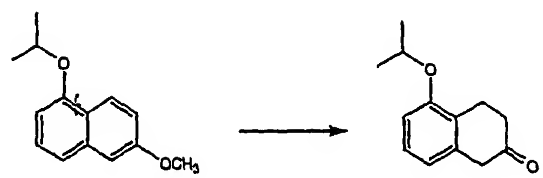
A mixture of 6-methoxy-1-tetralone (5.07 g, 28.8 mmole), 10% Pd/C (3.53 g, 3.32 mmole) in dry *p*-cymene (250 ml) was heated to reflux under argon for 38 hours. The reaction mixture was cooled to room temperature, filtered over celite and the residue rinsed thoroughly with *p*-cymene. The filtrate and the washings were combined and extracted twice with 1N sodium hydroxide solution (2 x 70 ml). The combined aqueous extracts were acidified with 6N hydrochloric acid to pH ~3 and extracted three times with ether. The combined organic layers were washed with water, dried over anhydrous sodium sulfate. Filtration and concentration gave crude 5-hydroxy-6-methoxynaphthalene (2.31 g, 46% yield) as a light brown solid which was used in the next step without further purification. LRMS (Electrospray): $C_{11}H_{10}O_2$, calc. 174; observed: 173 (M-H).

Step 2:



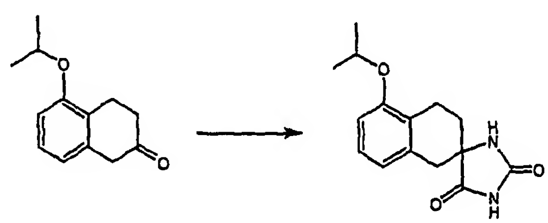
A mixture of 5-hydroxy-6-methoxynaphthalene (2.10 g, 12.1 mmole), cesium carbonate (19.7 g, 60.5 mmole), N,N-dimethylformamide (12 ml) and 2-bromopropane (3.50 ml, 36.9 mmole) was stirred in a 40°C oil bath overnight. The reaction mixture was filtered and the solid residue was rinsed thoroughly with ethyl ether. The filtrate and the washings were combined and concentrated in vacuo to remove most of the solvents. The brown residue was partitioned between water and ether and the layers were separated. The ether layer was washed with water. The combined aqueous layers were back extracted with ether. The ether extracts were combined, washed with brine and dried over sodium sulfate. Filtration and concentration gave a crude which was purified by column chromatography (2.5 → 5% ethyl acetate/hexanes) to give 1-isopropoxy-6-methoxynaphthalene (2.23 g, 86% yield) as a light brown oil. ^1H NMR ($CDCl_3$) δ 8.17 (1H, d, phenyl), 7.05-7.38 (4H, m, phenyl), 6.72 (1H, dd, phenyl), 4.73 (1H, m, CH of iPr), 3.92 (3H, s, OCH_3), 1.42 (6H, d, 2 CH_3 of iPr).

Step 3:



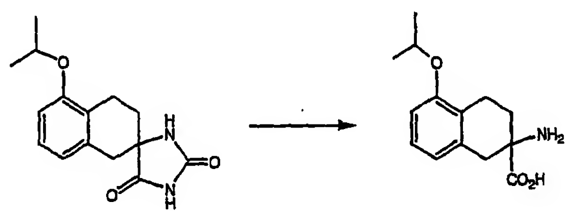
To a refluxing solution of 1-isopropoxy-6-methoxynaphthalene (2.23 g, 10.3 mmole) in absolute ethanol (50 ml) was carefully added small pieces of sodium metal (3.6 g, 157 mmole) over 45 minutes. The mixture was refluxed for a further 120 minutes. The reaction was cooled to room temperature, quenched with water and acidified with concentrated hydrochloric acid. The mixture was concentrated in vacuo to remove most of the ethanol. The aqueous mixture was extracted three times with ether. The combined organic layers were washed with water and dried over sodium sulfate. Filtration and concentration gave a reddish oil which was dissolved in 1:1 ethanol/water (90 ml), then *p*-toluenesulfonic acid (200 mg) was added. The mixture was refluxed for 60 minutes. After cooling to room temperature, most of the ethanol was removed under reduced pressure. The aqueous mixture was extracted twice with ether and the combined organic layers were washed with water, saturated sodium chloride solution and dried over sodium sulfate. Filtration and concentration gave a reddish oil which was purified by column chromatography (8 → 15 % ethyl acetate/hexanes) to give 5-isopropoxy-β-tetralone (1.37 g, 65% yield) as a colorless oil. ^{1}H NMR ($CDCl_3$) δ 7.16 (1H, t, phenyl), 6.78 (1H, d, phenyl), 6.71 (1H, d, phenyl), 4.53 (1H, m, CH of iPr), 3.56 (2H, s, benzylic), 3.08 (2H, t, benzylic), 2.50 (2H, t), 1.37 (6H, d, 2 CH_3 of iPr).

Step 4:



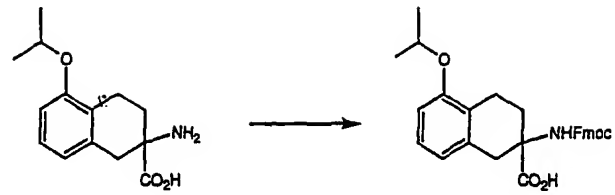
A mixture of 5-isopropoxy-β-tetralone (1.37 g, 6.71 mmole), potassium cyanide (660 mg, 10.1 mmole), ammonium carbonate (3.87 g, 40.3 mmole), ethanol (44 ml) and water (9 ml) in a sealed, thick walled pressure flask was heated in a 80°C oil bath for 42 hours. After cooling to room temperature, the slurry was poured into ice-water and stirred at room temperature for a couple of hours. Filtration followed by air-drying gave hydantoin (1.64 g, 89%).

Step 5:



A mixture of hydantoin (1.64 g, 5.98 mmole), $Ba(OH)_2 \cdot H_2O$ (5.66 g, 29.9 mmole) in water (25 ml) in a sealed, thick walled pressure flask was heated in a 100°C oil bath for 70 hours. The reaction mixture was cooled to room temperature, neutralized to ~ pH 7 using 4N sulfuric acid while being stirred vigorously. The suspension was stirred in a boiling water bath for one hour and cooled to room temperature. Basified with 1N sodium hydroxide solution and the white suspension was filtered and the precipitates rinsed with water. The combined filtrate and washings were concentrated in vacuo to ~ 75 ml. Neutralization with concentrated hydrochloric acid solution gave white precipitate which were filtered, washed with water and air-dried to give racemic 5-isopropoxy-2-aminotetraline-2-carboxylic acid (3.48 g, wet and containing inorganic salt, > quantitative yield). LRMS (Electrospray): $C_{14}H_{19}NO_3$, calc. 249; observed: 248 (M-H).

Step 6:



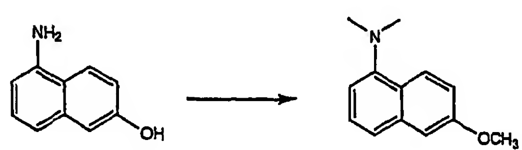
A mixture of racemic 5-isopropoxy-2-aminotetraline-2-carboxylic acid (3.48 g, 5.98 mmole theoretical), triethylamine (1.10 ml, 7.89 mmole), 9-fluorenylmethyl succinimidyl carbonate (Fmoc-OSu, 2.62 g, 7.77 mmole) in acetonitrile (30 ml) and water (30 ml) was stirred at room temperature for one day. TLC analysis of the reaction indicated the presence of starting material amino acid. 9-fluorenylmethyl succinimidyl carbonate (500 mg) was added and the mixture was stirred at room temperature for another day. The reaction mixture was concentrated in vacuo to remove most of the acetonitrile, acidified to pH ~3 with 10% aqueous citric acid solution, and the white emulsion extracted three times with methylene chloride. The combined organic layers were washed with water, brine, dried over magnesium sulfate. Filtration and concentration gave a crude oil which was purified by column chromatography (eluted with 1 → 2 → 5 → 8% methanol/methylene chloride) to give racemic Fmoc-5-isopropoxy-2-aminotetraline-2-carboxylic acid (0.50 g, 18% yield over 2 steps) as a white solid. HRMS (FAB): $C_{29}H_{30}NO_5$ (M+H) calc. 472.2124; observed: 472.2117.

EXAMPLE 14

Preparation of

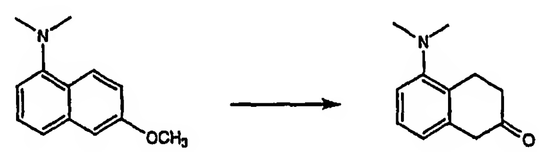
Fmoc-(D,L)-5-dimethylamino-2-aminotetraline-2-carboxylic acid (**Fmoc-(D,L) 5-DmaAtc-OH**)

Step 1:



A mixture of 5-amino-2-naphthol (2.97 g, 18.6 mmole), potassium carbonate (37.0 g, 268 mmole), acetone (100 ml) and iodomethane (10.0 ml, 161 mmole) was refluxed for 2 days. The reaction mixture was cooled to room temperature, filtered and the solid residue was rinsed thoroughly with ethyl ether and acetone. The filtrate and the washings were combined and concentrated in vacuo to remove most of the solvents. The brown residue was partitioned between water and ether and the layers were separated. The ether layer was washed with water. The combined aqueous layers were back extracted with ether. The ether extracts were combined, washed with brine and dried over sodium sulfate. Filtration and concentration gave crude 1-dimethylamino-6-methoxynaphthalene (3.54 g, 94% yield), as a dark brown oil. ^{1}H NMR ($CDCl_3$) δ 8.16 (1H, t, phenyl), 7.30-7.50 (2H, m, aromatic), 7.10-7.20 (2H, m, aromatic), 6.96 (1H, d, aromatic), 3.93 (3H, s, OCH_3), 2.89 (6H, s, $N(CH_3)_2$).

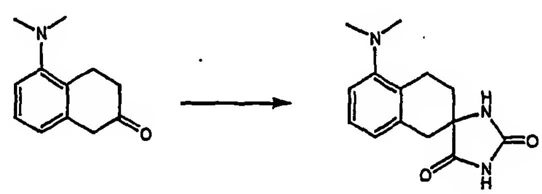
Step 2:



To a refluxing solution of 1-dimethylamino-6-methoxynaphthalene (2.99 g, 14.9 mmole) in absolute ethanol (100 ml) was carefully added small pieces of sodium metal (5.76 g, 251 mmole) over 45 minutes. The mixture was refluxed for another 45 minutes. TLC indicated the presence of unreacted starting material. Extra sodium metal (7.09 g, 308 mmole) was added and the reaction mixture was refluxed until TLC indicated the complete consumption of all the starting material. The reaction was cooled to room temperature and pH adjusted to ~ 9-10 with concentrated hydrochloric acid. The mixture was concentrated in vacuo to remove most of the ethanol. The aqueous mixture was extracted four times with ethyl acetate. The combined organic layers were washed with saturated sodium bicarbonate and dried over sodium sulfate. Filtration and concentration gave a dark brown oil which was dissolved in 1:1 ethanol/water (150 ml), then *p*-toluenesulfonic acid (3.05 g) was added to bring the pH to ~ 2-3. The mixture was refluxed for 3 hours. After cooling to room temperature, most of the ethanol was removed under reduced pressure. The pH of the

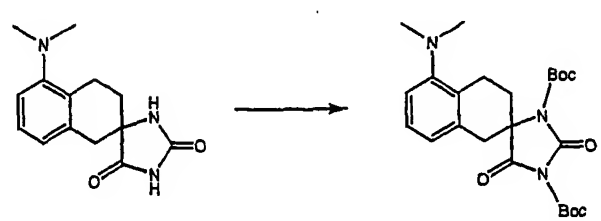
mixture was adjusted to ~ 9-10 with 2N sodium hydroxide solution and the aqueous mixture was extracted four times with ethyl acetate. The combined organic layers were washed with saturated sodium bicarbonate solution and dried over sodium sulfate. Filtration and concentration gave a dark brown oil which was purified by column chromatography (15 % ethyl acetate/hexanes) to give 5-dimethylamino-β-tetralone (834 mg, 30% yield) as a brown oil. ^{1}H NMR ($CDCl_3$) δ 7.18 (1H, t, phenyl), 6.96 (1H, d, phenyl), 6.82 (1H, d, phenyl), 3.57 (2H, s, benzylic), 3.10 (2H, t, benzylic), 2.70 (6H, s, $N(CH_3)_2$), 2.48 (2H, t). LRMS (Electrospray): $C_{12}H_{15}NO$, calc. 189; observed: 190 (M+H).

Step 3:



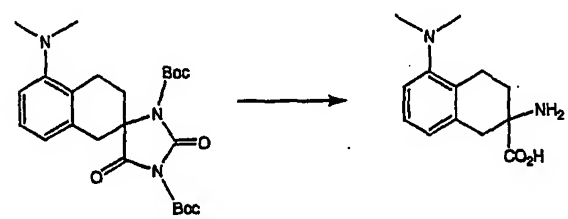
A mixture of 5-dimethylamino-β-tetralone (0.97 g, 5.13 mmole), potassium cyanide (510 mg, 7.82 mmole), ammonium carbonate (2.98 g, 31.0 mmole), ethanol (40 ml) and water (10 ml) in a sealed, thick walled pressure flask was heated in a 80°C oil bath for 29 hours. After cooling to room temperature, the dark brown slurry was poured into ice-water and stirred at room temperature for a couple of hours. Filtration followed by air-drying gave hydantoin (885 mg, 67%) as a dark brown solid. LRMS (Electrospray): $C_{14}H_{17}N_3O_2$, calc. 259; observed: 260 (M+H), 258 (M-H).

Step 4:



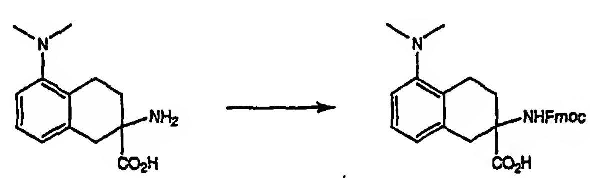
To a solution of hydantoin (832 mg, 3.21 mmole) in THF (25 ml) was added di-*t*-butyl dicarbonate (2.51 g, 11.5 mmole), triethylamine (0.50 ml, 3.59 mmole) and 4-dimethylaminopyridine (17 mg, 0.14 mmole). The mixture was stirred at room temperature overnight. The solvents were removed in vacuo and the crude was purified using column chromatography (15% ethyl acetate/hexanes) to give bis-Boc hydantoin (1.02 g, 69% yield) as a yellow foam. LRMS (Electrospray): $C_{24}H_{33}N_3O_6$, calc. 459; observed: 919 (2M+H).

Step 5:



To a solution of bis-Boc hydantoin (988 mg, 2.15 mmole) in dimethoxyethane (15 ml) was added 1N sodium hydroxide solution (20 ml). The mixture was stirred at room temperature overnight. The reaction mixture was concentrated in vacuo to remove most of the solvents and water was added to the resulting light brown mixture. The aqueous mixture was extracted twice with methylene chloride and twice with ethyl acetate. The aqueous layer was concentrated to ~ 20 ml, neutralized to pH ~7 with 1N hydrochloric acid to give a slurry. The slurry was filtered to give racemic 5-dimethylamino-2-aminotetraline-2-carboxylic acid (1.33 g, still wet, > quantitative yield) as a off-white solid. LRMS (Electrospray): $C_{13}H_{18}N_2O_2$, calc. 234; observed: 235 (M+H).

Step 6:



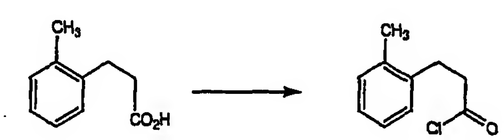
A mixture of 5-dimethylamino-2-aminotetraline-2-carboxylic acid (1.33 g, 2.15 mmole theoretical), triethylamine (0.40 ml, 2.87 mmole), 9-fluorenylmethyl succinimidyl carbonate (Fmoc-OSu, 0.92 g, 2.73 mmole) in acetonitrile (10 ml) and water (10 ml) was stirred at room temperature for one day. TLC analysis of the reaction indicated the presence of starting material amino acid. 9-fluorenylmethyl succinimidyl carbonate (400 mg) and triethylamine (0.2 ml) were added and the mixture was stirred at room temperature for another day. The reaction mixture was concentrated in vacuo to remove most of the acetonitrile and the almost neutral mixture was extracted three times with ethyl acetate. The combined organic layers were washed with water, brine, dried over sodium sulfate. Filtration and concentration gave a crude which was purified by column chromatography (eluted with 2.5 → 6 → 10 → 15 → 20% methanol/methylene chloride) to give racemic Fmoc-5-dimethylamino-2-aminotetraline-2-carboxylic acid (602 mg, 61% yield over 2 steps) as an off-white solid. HRMS (FAB): $C_{28}H_{28}N_2O_4$ (M) calc. 456.2049; observed: 456.2056.

EXAMPLE 15

Preparation of

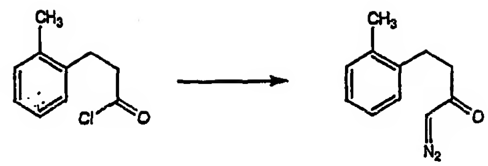
Fmoc-(D,L)-5-methyl-2-aminotetraline-2-carboxylic acid **(Fmoc-(D,L) 5-MeAtc-OH)**

Step 1:



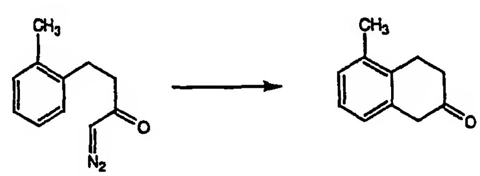
A mixture of 2-methylhydrocinnamic acid (3.0 g, 18.3 mmole), oxalyl chloride (3.19 ml, 36.6 mmole) and methylene chloride (30 ml) was cooled in an ice bath and N,N-dimethylformamide (0.14 ml, 1.81 mmole) was added dropwise. The mixture was stirred at room temperature overnight. Concentration in vacuo gave 3-(2-methylphenyl)propanoyl chloride which was taken up in methylene chloride and used in the next step as a crude.

Step 2:



A solution of the above acid chloride (crude, 18.3 mmole) in methylene chloride was slowly added to a solution of diazomethane (generated from 11.9 g of 1-methyl-3-nitro-1-nitrosoguanidine) in ether (80 ml) cooled in an ice bath. The mixture was then warmed up to room temperature and stirred overnight. The mixture was concentrated in vacuo and purified by column chromatography (10 → 20% ethyl acetate/hexanes) to give 1-diazo-4-(2-methylphenyl)butan-2-one (2.08 g, 60% over 2 steps) as a bright yellow oil.

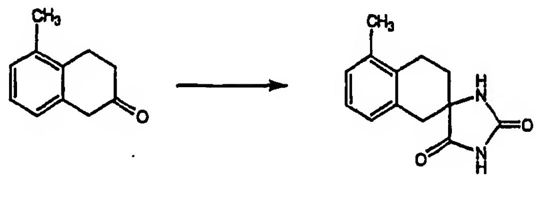
Step 3:



To a mixture of rhodium (II) acetate dimer (24 mg, 0.109 mmole) in methylene chloride (200 ml) under reflux was slowly added a solution of 1-diazo-4-(2-methylphenyl)butan-2-one (2.08 g, 11.1 mmole) in methylene chloride (50 ml) over 180 minutes. After the addition was complete, the mixture was refluxed for an extra twenty minutes. The mixture was cooled to room temperature, trifluoroacetic acid (2.40 ml) was added and the mixture was stirred at room temperature for an hour. The reaction was quenched with saturated sodium bicarbonate solution. The layers were separated and the methylene chloride layer was washed once more with saturated sodium bicarbonate solution. The combined aqueous layers were back-extracted with methylene chloride. The combined organic layers were dried over magnesium sulfate, filtered and concentrated in vacuo to give a crude brown oil. Purification by column chromatography (15% ethyl acetate/hexanes) gave 5-methyl-β-

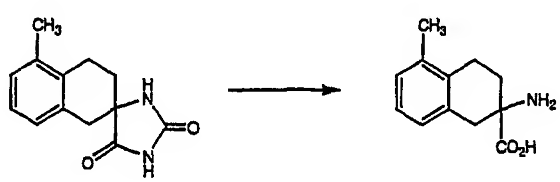
tetralone (1.48 g, 84% yield) as a light brown oil. ^{1}H NMR ($CDCl_3$) δ 6.90-7.20 (3H, m, phenyl), 3.58 (2H, s, benzylic), 3.03 (2H, t, benzylic), 2.55 (2H, t), 2.34 (3H, s, CH_3).

Step 4:



A mixture of 5-methyl-β-tetralone (1.48 g, 9.24 mmole), potassium cyanide (902 mg, 13.9 mmole), ammonium carbonate (5.33 g, 55.5 mmole), ethanol (45 ml) and water (9 ml) in a sealed, thick walled pressure flask was heated in a 80°C oil bath for 3 days. After cooling to room temperature, the slurry was poured into ice-water and stirred at room temperature for a couple of hours. Filtration followed by air-drying gave crude hydantoin (1.81 g, 85% yield) as a beige solid. ^{1}H NMR (DMSO-d_6) δ 10.66 (1H, broad s, NH), 8.22 (1H, broad s, NH), 6.85-7.05 (3H, m, phenyl), 2.17 (3H, s, CH_3).

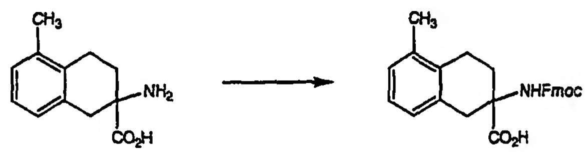
Step 5:



A mixture of hydantoin (1.80 g, 7.82 mmole), $Ba(OH)_2$. H_2O (7.40 g, 39.1 mmole) in water (28 ml) in a sealed, thick walled pressure flask was heated in a 125°C oil bath for 88 hours. The reaction mixture was cooled to room temperature, acidified to ~ pH 3 using 4N sulfuric acid while being stirred vigorously. The suspension was stirred in a boiling water bath for an hour and cooled to room temperature. The white suspension was filtered and the precipitates rinsed with water. The combined filtrate and washings were concentrated in vacuo to ~ 50

ml. Neutralization with concentrated ammonium hydroxide solution gave white precipitate which were filtered, washed with water and air-dried to give racemic 5-methyl-2-aminotetraline-2-carboxylic acid (1.05 g, 65% yield) as a beige solid. LRMS (Electrospray): $C_{12}H_{15}NO_2$, calc. 205; observed: 206 (M+H).

Step 6:



A mixture of racemic 5-methyl-2-aminotetraline-2-carboxylic acid (1.05 g, 5.12 mmole), triethylamine (0.93 ml, 6.67 mmole), 9-fluorenylmethyl succinimidyl carbonate (Fmoc-OSu, 2.24 g, 6.64 mmole) in acetonitrile (30 ml) and water (30 ml) was stirred at room temperature for 2 days. TLC analysis of the reaction indicated the presence of starting material amino acid. 9-fluorenylmethyl succinimidyl carbonate (520 mg) was added and the mixture was stirred at room temperature for another 24 hours. The reaction mixture was concentrated in vacuo to remove most of the acetonitrile, acidified to pH ~3 with 10% aqueous citric acid solution, and the white emulsion was extracted twice with methylene chloride. The combined organic layers were washed with water, brine and dried over magnesium sulfate. Filtration and concentration gave a crude oil which was purified by column chromatography (eluted with 2 → 5→ 8% methanol/methylene chloride) to give racemic Fmoc-5-methyl-2-aminotetraline-2-carboxylic acid (1.62 g, 74% yield) as an light brown solid. HRMS (FAB): $C_{27}H_{26}NO_4$ (M+H) calc. 428.1862; observed: 428.1844.

EXAMPLE 16

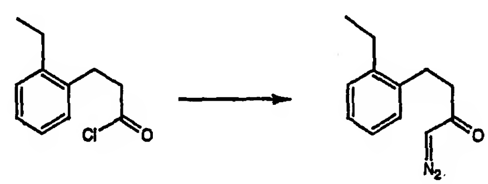
Preparation of

Fmoc-(D,L)-5-ethyl-2 aminotetraline-2-carboxylic acid (Fmoc-(D,L) 5-EtAtc-OH)

Step 1:

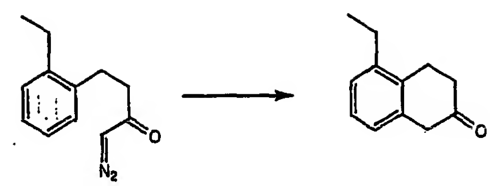
A mixture of 3-(2-ethylphenyl)propanoic acid (prepared in 3 steps from 1-ethyl-2-iodobenzene, 4.24 g, 23.8 mmole), thionyl chloride (9.50 ml, 130 mmole) and toluene (100 ml) was refluxed for 2 hours. Concentration in vacuo gave 3-(2-ethylphenyl)propanoyl chloride which was taken up in methylene chloride and used in the next step as a crude.

Step 2:



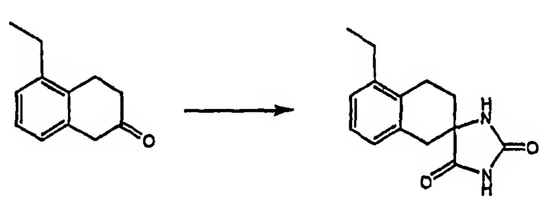
A solution of the above acid chloride (crude, 23.8 mmole) in methylene chloride was slowly added to a solution of diazomethane (generated from 15.6 g of 1-methyl-3-nitro-1-nitrosoguanidine) in ether (100 ml) cooled in an ice bath. The mixture was then warmed up to room temperature and stirred overnight. The mixture was concentrated in vacuo and purified by column chromatography (10 → 20% ethyl acetate/hexanes) to give 1-diazo-4-(2-ethylphenyl)butan-2-one (3.47 g, 72% over 2 steps). ^{1}H NMR ($CDCl_3$) δ 7.1-7.25 (4H, m, phenyl), 5.21 (1H, broad s, diazo), 2.97 (2H, m, CH_2 of ethyl), 1.20 (3H, t, CH_3).

Step 3:



To a mixture of rhodium (II) acetate dimer (38 mg, 0.172 mmole) in methylene chloride (300 ml) under reflux was slowly added a solution of 1-diazo-4-(2-ethylphenyl)butan-2-one (3.47 g, 17.2 mmole) in methylene chloride (50 ml) over 90 minutes. After the addition was complete, the mixture was refluxed for an extra twenty minutes. The mixture was cooled to room temperature, trifluoroacetic acid (3.75 ml) was added and the mixture was stirred at room temperature for an hour. The reaction was quenched with saturated sodium bicarbonate solution. The layers were separated and the methylene chloride layer was washed once more with saturated sodium bicarbonate solution. The combined aqueous layers were back-extracted with methylene chloride. The combined organic layers were dried over magnesium sulfate, filtered and concentrated in vacuo to give crude 5-ethyl-β-tetralone (3.09 g, > quantitative yield) as a reddish-brown oil. The compound was used in the next step without further purification. ^{1}H NMR ($CDCl_3$) δ 6.9-7.2 (3H, m, phenyl), 3.58 (2H, s, benzylic), 3.08 (2H, s, benzylic), 2.70 (2H, q, CH_2 of ethyl), 2.52 (2H, t, benzylic), 1.20 (3H, t, CH_3 of ethyl).

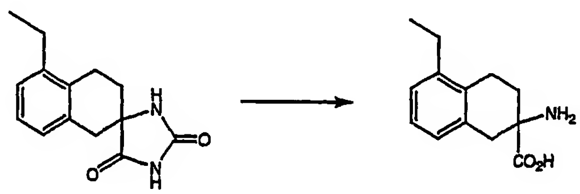
Step 4:



A mixture of 5-ethyl-β-tetralone (3.09 g, 17.7 mmole), potassium cyanide (1.73 g, 26.6 mmole), ammonium carbonate (10.2 g, 106 mmole), ethanol (80 ml) and water (16 ml) in a

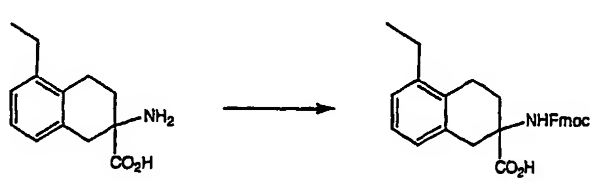
sealed, thick walled pressure flask was heated in a 80°C oil bath for 48 hours. After cooling to room temperature, the white slurry was poured into ice-water and stirred at room temperature for a couple of hours. Filtration followed by air-drying gave hydantoin (3.85 g, 92% yield over 2 steps) as a light beige solid. ^{1}H NMR (DMSO-d_6) δ 10.67 (1H, broad s, NH), 8.26 (1H, broad s, NH), 6.8-7.1 (3H, m, phenyl), 1.13 (3H, t, CH_3). LRMS (Electrospray): $C_{14}H_{16}N_2O_2$, calc. 244; observed: 243 (M-H).

Step 5:



A mixture of hydantoin (1.00 g, 4.09 mmole), $Ba(OH)_2$. H_2O (4.00 g, 21.1 mmole) in water (20 ml) in a sealed, thick walled pressure flask was heated in a 125°C oil bath for 48 hours. The reaction mixture was cooled to room temperature, acidified to ~ pH 3 using 4N sulfuric acid while being stirred vigorously. The suspension was stirred in a boiling water bath for two hours and cooled to room temperature. The white suspension was filtered and the precipitates rinsed with water. The combined filtrate and washings were concentrated in vacuo to ~ 50 ml. Neutralization with concentrated ammonium hydroxide solution gave white precipitate which were filtered, washed with water and dried in vacuo overnight to give racemic 5-ethyl-2-aminotetraline-2-carboxylic acid (796 mg, 89% yield). LRMS (Electrospray): $C_{13}H_{17}NO_2$, calc. 219; observed: 220 (M+H).

Step 6:



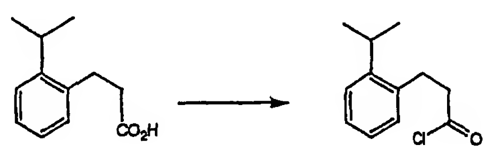
A mixture of racemic 5-ethyl-2-aminotetraline-2-carboxylic acid (765 mg, 3.49 mmole), triethylamine (1.0 ml, 7.17 mmole), 9-fluorenylmethyl succinimidyl carbonate (Fmoc-OSu, 1.79 g, 5.31 mmole) in acetonitrile (40 ml) and water (40 ml) was stirred at room temperature for 2 days. The reaction mixture was concentrated in vacuo to remove most of the acetonitrile, acidified to pH ~3 with 10% aqueous citric acid solution, and the white emulsion extracted twice with methylene chloride, twice with ethyl acetate. The methylene chloride extracts were washed with water, brine and dried over magnesium sulfate. The ethyl acetate extracts were washed with water, brine and dried over magnesium sulfate. Filtration, and concentration gave a crude oil which was purified by column chromatography (eluted with 2 → 5→ 8% methanol/methylene chloride) to give racemic Fmoc-5-ethyl-2-aminotetraline-2-carboxylic acid (330 mg, 21% yield) as a white solid. HRMS (FAB): $C_{28}H_{28}NO_4$ (M+H) calc. 442.2018; observed: 442.2010.

EXAMPLE 17

Preparation of

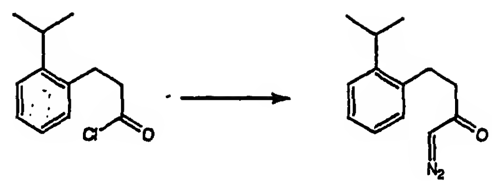
Fmoc-(D,L)-5-isopropyl-2-aminotetraline-2-carboxylic acid **(Fmoc-(D,L) 5-iPrAtc-OH)**

Step 1:



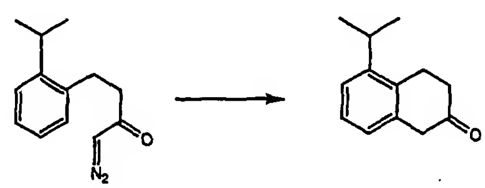
A mixture of 3-(2-isopropylphenyl)propanoic acid (prepared in 3 steps from 1-isopropyl-2-iodobenzene, 2.01 g, 10.5 mmole), thionyl chloride (4.30 ml, 59.0 mmole) and toluene (40 ml) was refluxed for 2 hours. Concentration in vacuo gave 3-(2-isopropylphenyl)propanoyl chloride which was taken up in methylene chloride and used in the next step as a crude.

Step 2:



A solution of the above acid chloride (crude, 10.5 mmole) in methylene chloride was slowly added to a solution of diazomethane (generated from 6.95 g of 1-methyl-3-nitro-1-nitrosoguanidine) in ether (50 ml) cooled in an ice bath. The mixture was then warmed up to room temperature and stirred overnight. The mixture was concentrated in vacuo and purified by column chromatography (20% ethyl acetate/hexanes) to give 1-diazo-4-(2-isopropylphenyl)butan-2-one (1.87 g, 82% over 2 steps) as a bright yellow oil. ^{1}H NMR ($CDCl_3$) δ 7.10-7.30 (4H, m, phenyl), 5.21 (1H, broad s, diazo), 3.15 (1H, m, CH of iPr), 3.00 (2H, t, benzylic), 2.57 (2H, m), 1.24 (6H, d, 2 CH_3 of iPr).

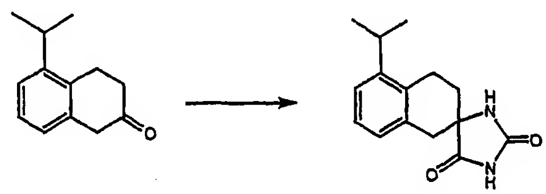
Step 3:



To a mixture of rhodium (II) acetate dimer (20 mg, 0.091 mmole) in methylene chloride (160 ml) under reflux was slowly added a solution of 1-diazo-4-(2-bromophenyl)butan-2-one (1.87 g, 8.65 mmole) in methylene chloride (25 ml) over 60 minutes. After the addition was complete, the mixture was refluxed for an extra fifteen minutes. The mixture was cooled to room temperature, trifluoroacetic acid (1.90 ml) was added and the mixture was stirred at room temperature for 45 minutes. The reaction was quenched with saturated sodium bicarbonate solution. The layers were separated and the methylene chloride layer was washed once more with saturated sodium bicarbonate solution. The combined aqueous

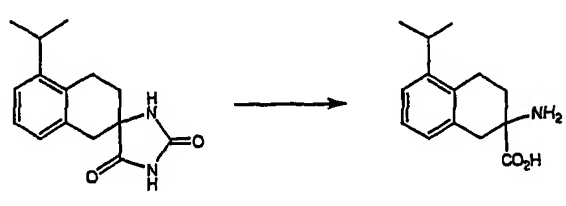
layers were back-extracted with methylene chloride. The combined organic layers were dried over magnesium sulfate, filtered and concentrated in vacuo to give a crude brown oil. Purification by column chromatography (5% ethyl acetate/hexanes) gave 5-isopropyl-β-tetralone (1.57 g, 96% yield) as a light yellow oil. ^{1}H NMR ($CDCl_3$) δ 6.93-7.22 (3H, m, phenyl), 3.59 (2H, s, benzylic), 3.24 (1H, m, CH of iPr), 3.12 (2H, t, benzylic), 2.52 (2H, t), 1.27 (6H, d, 2 CH_3 of iPr).

Step 4:



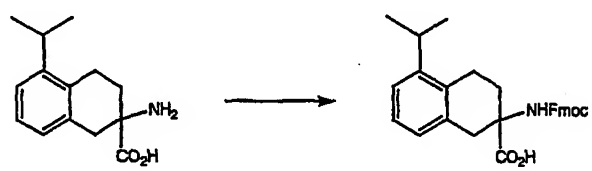
A mixture of 5-isopropyl-β-tetralone (1.57 g, 8.34 mmole), potassium cyanide (0.82 g, 12.6 mmole), ammonium carbonate (4.81 g, 50.1 mmole), ethanol (40 ml) and water (10 ml) in a sealed, thick walled pressure flask was heated in a 80°C oil bath for 48 hours. After cooling to room temperature, the brown slurry was poured into ice-water and stirred at room temperature for a couple of hours. Filtration followed by air-drying gave crude hydantoin as a beige solid which was used in the next step without further purification. ^{1}H NMR (DMSO-d_6) δ 10.69 (1H, broad s, NH), 8.30 (1H, broad s, NH), 6.85-7.32 (3H, m, phenyl), 1.15 (6H, t, CH_3). LRMS (Electrospray): $C_{15}H_{18}N_2O_2$, calc. 258; observed: 539 (2M+Na).

Step 5:



A mixture of hydantoin (crude, 8.34 mmole theoretical), $Ba(OH)_2$. H_2O (7.90 g, 41.7 mmole) in water (40 ml) in a sealed, thick walled pressure flask was heated in a 125°C oil bath for 38 hours. The reaction mixture was cooled to room temperature, acidified to ~ pH 3 using 4N sulfuric acid while being stirred vigorously. The suspension was stirred in a boiling water bath for two hours and cooled to room temperature. The white suspension was filtered and the precipitates rinsed with water. The combined filtrate and washings were concentrated in vacuo to ~ 50 ml. Neutralization with concentrated ammonium hydroxide solution gave white precipitate which were filtered, washed with water and dried in vacuo overnight to give racemic 5-isopropyl-2-aminotetraline-2-carboxylic acid (1.23 g, 63% yield over 2 steps) as a beige solid. LRMS (Electrospray): $C_{14}H_{19}NO_2$, calc. 233; observed: 232 (M-H).

Step 6:



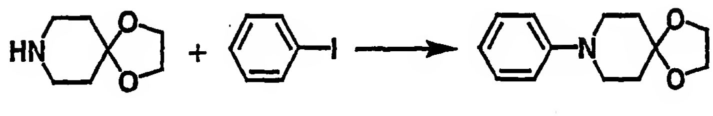
A mixture of racemic 5-isopropyl-2-aminotetraline-2-carboxylic acid (250 mg, 1.07 mmole), triethylamine (1.2 ml, 8.61 mmole), 9-fluorenylmethyl succinimidyl carbonate (Fmoc-OSu, 2.70 g, 8.00 mmole) in acetonitrile (30 ml) and water (30 ml) was stirred at room temperature for 2 days. The reaction mixture was concentrated in vacuo to remove most of the acetonitrile, acidified to pH ~3 with 10% aqueous citric acid solution, and the white emulsion was extracted with ethyl acetate. The organic layer was washed with water, brine and dried over sodium sulfate. Filtration and concentration gave a crude oil which was purified by column chromatography (eluted with 2 → 5→ 8% methanol/methylene chloride) to give racemic Fmoc-5-isopropyl-2-aminotetraline-2-carboxylic acid (208 mg, 43% yield) as an off-white foam. HRMS (FAB): $C_{29}H_{30}NO_4$ (M+H) calc. 456.2175; observed: 456.2184.

EXAMPLE 18

Preparation of

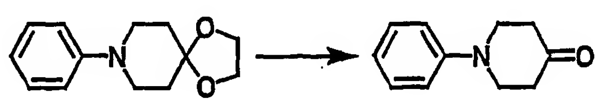
Fmoc-4-amino-1-phenylpiperidine-4-carboxylic acid **(Fmoc-Appc-OH)**

Step 1:



To a solution of iodobenzene (6.37 g, 3.5 mL, 31.2 mmole), 1,4-dioxa-8-azaspiro [4.5] decane (10.32 g, 9.3 mL, 72.2 mmole, 2.3 equiv) and sodium tert-butoxide (8.0 g, 83.3 mmole, 2.7 equiv) in dry dioxane (120 mL) were added tris(dibenzylideneacetone)dipalladium(0) (91 mg, 0.1 mmol) and tri-*o*-tolylphosphine (180 mg, 0.591 mmol). The reaction was heated at 90 ^{0}C for 26 hrs. The resulting reaction mixture was concentrated to remove solvent. The residue was treated with water and extracted with EtOAc. The combined organic extracts were combined, washed with brine, dried over Na_2SO_4 and concentrated to give a brown oil. This crude product was purified on flash chromatography (hexane/EtOAc, 95/5 to 75/25) to provide the pure product as a slightly yellow solid (6.08 g, 89%). ^{1}H NMR ($CDCl_3$), 7.25 (ddt, 2H), 6.95 (dd, 2H), 6.84 (t, 1H),4.00 (s, 4H), 3.32 (t, 4H) and 1.84 (t, 4H); MS (electrospray) *m/e* 220 (M+H), Calcd for $C_{13}H_{17}NO_2$, 219.

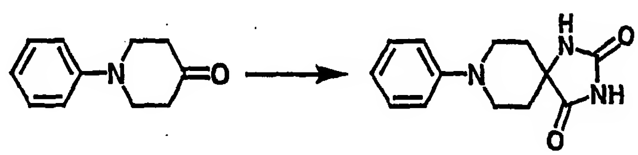
Step 2:



To a solution of the ketal (3.22 g, 15.16 mmol) in acetone (100 mL) was added 6N hydrochloric acid (50 mL) and the reaction was heated at reflux overnight. The resulting reaction mixture was concentrated to remove solvent. The residue was taken up in EtOAc and neutralized with aqueous 6N NaOH solution. The layers were separated and the aqueous

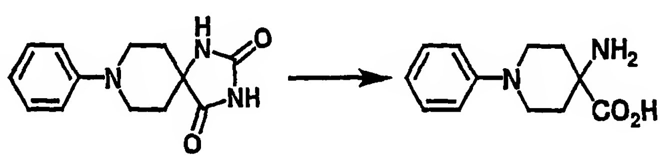
layer was extracted with EtOAc. The combined organic extracts were washed with brine, dried over Na_2SO_4 and concentrated. The crude product was purified on flash chromatography (hexane/EtOAc, 80/20→60/40) to give the product as a yellow oil (2.58 g, 97%). MS (electrospray) *m/e* 176 (M+H), Calcd for $C_{11}H_{13}NO$, 175.

Step 3:



To a solution of the ketone (2.53 g, 14.46 mmol) in ethanol (75 mL) and water (25 mL) in a glass pressure bottle, were added ammonium carbonate (12.9 g, 134.3 mmole, 9 equiv.) and potassium cyanide (2.11 g, 32.5 mmol, 2 equiv.). The mixture was heated at 80-90 ^{0}C for 18 hrs. The cooled reaction mixture was concentrated in vacuo and the residue was treated with water, extracted with EtOAc (4x). The combined organic extracts were washed with water, dried over anhydrous Na_2SO_4 and concentrated to give the spectroscopically pure hydantoin as a white solid (3.36 g, 95% yield). MS (electrospray) *m/e* 246 (M+H), Calcd for $C_{13}H_{15}N_3O_2$, 245.

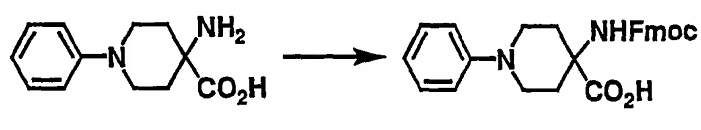
Step 4:



The hydantoin (3.36 g) was suspended in aqueous NaOH (6N, 100 mL) and heated at 130 ^{0}C for 2-3 days. Upon completion (by HPLC) of the hydrolysis, the reaction mixture was neutralized with conc. HCl to slightly acidic (pH ~6). The resulting slurry was filtered, washed with water and dried to give 4-amino-1-phenylpiperidine-4-carboxylic acid (APPC)

as a white solid (5.26 g, >100 % yield, wet and contaminated with inorganic salt), which showed a single peak on HPLC and used directly for the next step. MS (electrospray) *m/e* 221 (M+H), Calcd for $C_{12}H_{16}N_2O_2$, 220.

Step 5:



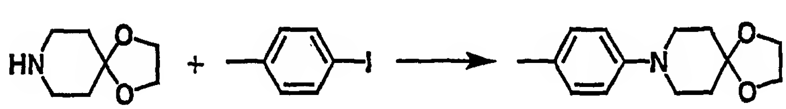
The crude amino acid APPC from the last step was suspended in dioxane (80 mL) and aqueous 10% Na_2CO_3 (40 ml), treated with Fmoc-Cl (5.3 g, 20.57 mmole, 1.5 equiv) and was stirred vigorously overnight. The reaction mixture was then concentrated to remove dioxane, neutralized with 6N HCl to slightly acidic (pH 6) and extracted with EtOAc. The combined organic extracts were washed with brine and dried over Na_2SO_4. Removal of the solvent gave the crude product which was purified on flash chromatography (hexane/EtOAc to CH_2Cl_2/MeOH) to give pure APPC (4.91 g, 81% overall yield for two steps). ^1H NMR(DMSO-d_6), 7.88 (d, 2H), 7.74 (d, 2H), 7.19-7.42 (m, 8H), 4.20-4.31 (m, 3H); HRMS m/z 465.1788, Calcd for $C_{27}H_{26}N_2O_4Na$, 465.1791

EXAMPLE 19

Preparation of

Fmoc-4-amino-1-(4-methylphenyl)piperidine-4-carboxylic acid (**Fmoc-4-MeAppc-OH**)

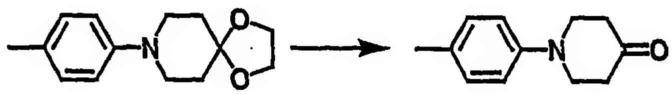
Step 1:



To a solution of 4-iodotoluene (2.12 g, 9.7 mmol), 1,4-dioxa-8-azaspiro[4.5]decane (2.8 mL, 3.12 g, 21.82 mmol, 2.2 equiv) and sodium tert-butoxide (2.6 g, 27.08 mmol, 2.8 equiv) in dry dioxane (40 mL) were added tris(dibenzylideneacetone)dipalladium (0) (44.4 mg, 0.0485

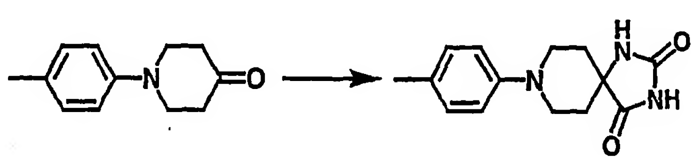
mmol) and tri-*o*-tolylphosphine (59.0 mg, 0.194 mmol). The reaction was heated at 90 ^{0}C for 26 hrs. The resulting reaction mixture was concentrated to remove solvent. The residue was treated with water and extracted with EtOAc. The combined organic extracts were combined, washed with brine, dried over Na_2SO_4 and concentrated to give brown oil. This crude product was purified on flash chromatography (hexane/EtOAc, 95/5 to 75/25) to provide the pure product as a slightly yellow solid (1.937 g, 85%). ^{1}H NMR ($CDCl_3$), 7.06 (d, 2H), 6.87 (d, 2H), 3.99 (s, 4H), 3.26 (t, 4H), 2.26 (s, 3H) and 1.85 (t, 4H).

Step 2:



To a solution of the ketal (1.58 g, 6.79 mmol) in acetone (50 mL) was added 6N hydrochloric acid (25 mL) and the reaction was heated at reflux overnight. The resulting reaction mixture was concentrated to remove solvent. The residue was taken up in EtOAc and neutralized with aqueous 6N NaOH solution. The layers were separated and the aqueous layer was extracted with EtOAc. The combined organic extracts were washed with brine, dried over Na_2SO_4 and concentrated. The crude product was purified on flash chromatography (hexane/EtOAc, 90/10→70/30) to give the product as a yellow oil (1.27 g, 98%). MS (electrospray) *m/e* 190 (M+H), Calcd for $C_{12}H_{15}NO$, 189.

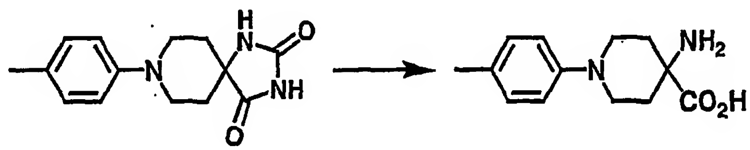
Step 3:



To a solution of the ketone (1.17 g, 6.18 mmol) in ethanol (60 mL) and water (20 mL) in a glass pressure bottle, were added ammonium carbonate (4.74 g, 49.44 mmole, 8 equiv.) and potassium cyanide (1.01 g, 15.54 mmol, 2.5 equiv.). The mixture was heated at 90 ^{0}C for 22

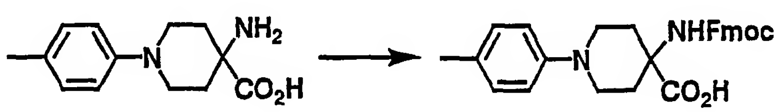
hrs. The cooled reaction mixture was concentrated in vacuo and the residue was treated with water, extracted with EtOAc (4x). The combined organic extracts were washed with water, dried over anhydrous Na_2SO_4 and concentrated to give the spectroscopically pure hydantoin as a white solid (1.554 g, 97% yield). MS (electrospray) *m/e* 260 (M+H), Calcd for $C_{14}H_{17}N_3O_2$, 259.

Step 4:



The hydantoin (1.502 g) was suspended in aqueous NaOH (6N, 40 mL) and heated at 130 ^{0}C for 4 days. Upon completion (by HPLC) of the hydrolysis, the reaction mixture was neutralized with conc. HCl to slightly acidic (pH ~6). The resulting slurry was filtered, washed with water and dried to give 4-amino-1-(4-methylphenyl)piperidine-4-carboxylic acid (4-MeAPPC) as a white solid (2.10 g, >100 % yield, wet and contaminated with inorganic salt), which showed a single peak on HPLC and used directly in the next step. MS (electrospray) *m/e* 235 (M+H), Calcd for $C_{13}H_{18}N_2O_2$, 234.

Step 5:



The crude amino acid 4-MeAPPC from the last step was suspended in dioxane (80 mL) and aqueous 10% Na_2CO_3 (40 ml), treated with Fmoc-Cl (2.2 g, 8.59 mmole, 1.5 equiv) and was stirred vigorously overnight. The reaction mixture was then concentrated to remove dioxane, neutralized with 6N HCl to slightly acidic (pH 6) and extracted with EtOAc. The combined organic extracts were washed with brine and dried over Na_2SO_4. Removal of the solvent

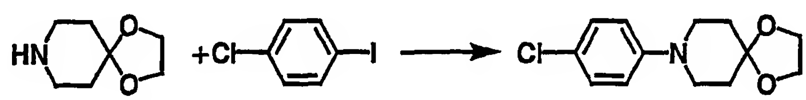
gave the crude product which was purified on flash chromatography (hexane/EtOAc to CH_2Cl_2/MeOH) to give pure Fmoc-4-MeAPPC (2.16 g, 82% overall yield for two steps). ^1H NMR (DMSO-d_6): 7.88 (d, 2H), 7.72 (d, 2H), 7.39 (t, 2H), 7.30 (td, 2H), 6.99 (d, 2H), 6.82 (d, 2H), 2.18 (s, 3H); MS (electrospray) *m/e* 457 (M+H), Calcd for $C_{28}H_{28}N_2O_4$, 456.

EXAMPLE 20

Preparation of

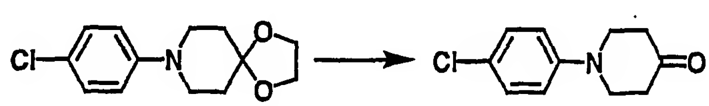
Fmoc-4-amino-1-(4-chlorophenyl)piperidine-4-carboxylic acid (**Fmoc-4-ClAppc-OH**)

Step 1:



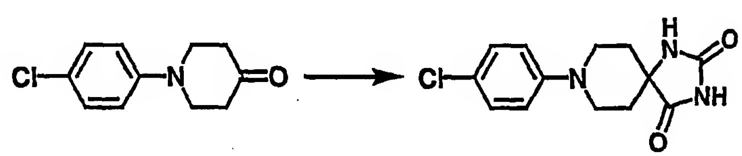
To a solution of 1-chloro-4-iodobenzene (2.38 g, 10.0 mmole), 1,4-dioxa-8-azaspiro [4.5] decane (3.1 mL, 3.44 g, 24.0 mmole, 2.4 equiv) and sodium tert-butoxide (2.68 g, 28.0 mmole, 2.8 equiv) in dry dioxane (40 mL) were added tris(dibenzylideneacetone)dipalladium(0) (45.5 mg, 0.0497 mmol) and tri-*o*-tolyl-phosphine (61 mg, 0.20 mmol). The reaction was heated at 90 ^{0}C for 9 hrs. The resulting reaction mixture was concentrated to remove solvent. The residue was treated with water and extracted with EtOAc. The combined organic extracts were combined, washed with brine, dried over Na2SO4 and concentrated to give a brown oil. This crude product was purified on flash chromatography (hexane/EtOAc, 95/5 to 75/25) to provide the pure product as a slightly yellow solid (2.17 g, 86%). ^1H NMR($CDCl_3$), 7.18 (dt, 2H), 6.85 (dt, 2H), 3.98 (s, 4H), 3.28 (t, 4H) and 1.82 (t, 4H).

Step 2:



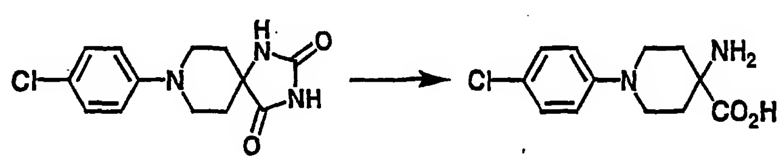
To a solution of the ketal (2.123 g, 8.39 mmole) in acetone (75 mL) was added 6N hydrochloric acid (30 mL) and the reaction was heated at reflux overnight. The resulting reaction mixture was concentrated to remove solvent. The residue was taken up in EtOAc and neutralized with aqueous 6N NaOH solution. The layers were separated and the aqueous layer was extracted with EtOAc. The combined organic extracts were washed with brine, dried over Na_2SO_4 and concentrated. The crude product was purified on flash chromatography (hexane/EtOAc, 95/5→70/30) to give the product as a yellow solid (1.515 g, 86%). MS (electrospray) *m/e* 210 (M+H), Calcd for $C_{11}H_{12}ClNO$, 209.

Step 3:



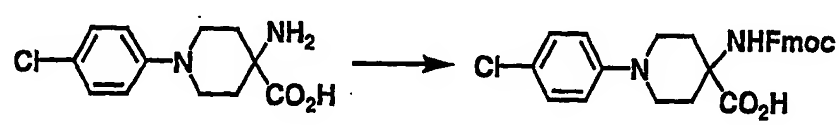
To a solution of the ketone (1.465 g, 6.986 mmole) in ethanol (75 mL) and water (25 mL) in a glass pressure bottle, were added ammonium carbonate (5.36 g, 55.88 mmole, 8 equiv.) and potassium cyanide (1.135 g, 17.46 mmol, 2.5 equiv.). The mixture was heated at 80-90 ^{0}C for 18 hrs. The cooled reaction mixture was concentrated in vacuo and the residue was treated with water, extracted with EtOAc (4x). The combined organic extracts were washed with water, dried over anhydrous Na_2SO_4 and concentrated to give the spectroscopically pure hydantoin as a white solid (1.817 g, 93% yield). MS (electrospray) *m/e* 280 (M+H), Calcd for $C_{13}H_{14}ClN_3O_2$, 279.

Step 4:



The hydantoin (1.768 g) was suspended in aqueous NaOH (6N, 50 mL) and heated at 130 ^{0}C for 4 days. Upon the completion (by HPLC) of the hydrolysis, the reaction mixture was neutralized with conc. HCl to slightly acidic (pH ~6). The resulting slurry was filtered, washed with water and dried to give 4-amino-1-(4-chlorophenyl)piperidine-4-carboxylic acid (4-ClAPPC) as a white solid (2.05 g, >100 % yield, wet and contaminated with inorganic salt), which showed a single peak on HPLC and used directly for the next step. MS (electrospray) *m/e* 253 (M-H), Calcd for $C_{12}H_{15}ClN_2O_2$, 254.

Step 5:



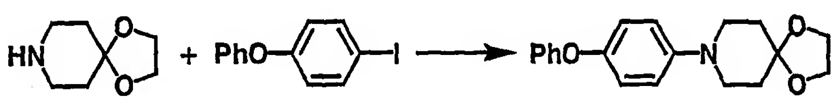
The crude amino acid 4-ClAPPC from the last step was suspended in dioxane (100 mL) and aqueous 10% Na_2CO_3 (50 ml), treated with Fmoc-Cl (2.0 g, 7.75 mmole, 1.2 equiv) and was stirred vigorously overnight. The reaction mixture was then concentrated to remove dioxane, neutralized with 6N HCl to slightly acidic (pH 6) and extracted with EtOAc. The combined organic extracts were washed with brine and dried over Na_2SO_4. Removal of the solvent gave the crude product which was purified on flash chromatography (hexane/EtOAc to CH_2Cl_2/MeOH) to give pure Fmoc-4-ClAPPC (1.18 g, 81% overall yield for two steps). ^{1}H NMR (DMSO-d_6): 7.87 (d, 2H), 7.71 (d, 2H), 7.39 (td, 2H), 7.30 (td, 2H), 7.20 (d, 2H), 6.92 (d, 2H), 3.44 (d, 2H), 2.93 (t, 2H); MS (electrospray) *m/e* 477 (M+H), Calcd for $C_{27}H_{25}N_2O_4$, 476.

EXAMPLE 21

Preparation of

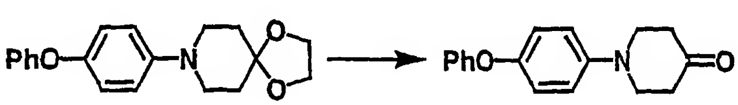
Fmoc-4-amino-1-(4-phenoxyphenyl)piperidine-4-carboxylic acid (Fmoc-4-PhOAppc-OH)

Step 1:



To a solution of 1-iodo-4-phenoxybenzene (3.15 g, 10.6 mmol), 1,4-dioxa-8-azaspiro [4.5] decane (3.3 mL, 3.66 g, 25.6 mmole, 2.4 equiv) and sodium tert-butoxide (2.85 g, 29.7 mmol, 2.8 equiv) in dry dioxane (40 mL) were added tris (dibenzylideneacetone) dipalladium (0) (48.5 mg, 0.053 mmol) and tri-*o*-tolyl- phosphine (64 mg, 0.4 mmol). The reaction was heated at 90 ^{0}C for 9 hrs. The resulting reaction mixture was concentrated to remove solvent. The residue was treated with water and extracted with EtOAc. The combined organic extracts were combined, washed with brine, dried over Na_2SO_4 and concentrated to give a brown oil. This crude product was purified on flash chromatography (hexane/EtOAc, 95/5 to 80/20) to provide the pure product as a slightly yellow solid (2.805, 85%). ^{1}H NMR ($CDCl_3$), 7.26-7.32 (m, 2H), 7.03 (t, 1H), 6.92-6.97 (m, 6H), 4.00 (s, 4H), 3.26 (t, 4H), 1.86 (t, 4H).

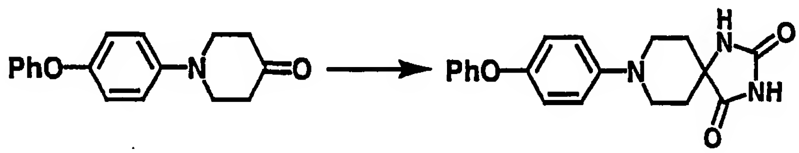
Step 2:



To a solution of the ketal (2.755 g, 8.86 mmol) in acetone (90 mL) was added 6N hydrochloric acid (45 mL) and the reaction was heated at reflux overnight. The resulting reaction mixture was concentrated to remove solvent. The residue was diluted with EtOAc and neutralized with aqueous 6N NaOH. The layers were separated and the aqueous layer was extracted with EtOAc. The combined organic extracts were washed with brine, dried

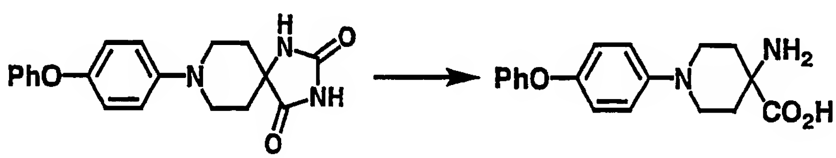
over Na_2SO_4 and concentrated to give the crude product which was purified on flash chromatography (hexane/EtOAc, 90/10 to 70/30) to give the product as a yellow oil (2.21 g, 93%). MS (electrospray) *m/e* 268 (M+H), Calcd for $C_{17}H_{17}ClNO_2$, 267.

Step 3:



To a solution of the ketone (2.01 g, 7.52 mmol) in ethanol (80 mL) and water (25 mL) in a glass pressure bottle, were added ammonium carbonate (5.78 g, 60.0 mmol, 8 equiv.) and potassium cyanide (1.22 g, 18.80 mmol, 2.5 equiv.). The mixture was heated at 80-90 ^{0}C for 18 hrs. The cooled reaction mixture was concentrated in vacuo and the residue was treated with water, extracted with EtOAc (4x). The combined organic extracts were washed with water, dried over anhydrous Na_2SO_4 and concentrated to give the spectroscopically pure hydantoin as a white solid (2.34 g, 95% yield). MS (electrospray) *m/e* 338 (M+H), Calcd for $C_{19}H_{19}N_3O_3$, 337.

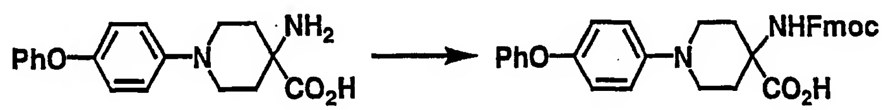
Step 4:



The hydantoin (2.28 g, 6.76 mmole) was suspended in aqueous NaOH (6N, 60 mL) and heated at 130 ^{0}C for 4 days. Upon completion (by HPLC) of the hydrolysis, the reaction mixture was neutralized with conc. HCl to slightly acidic (pH ~6). The resulting slurry was filtered, washed with water and dried to give 4-amino-1-(4-phenoxyphenyl)piperidine-4-carboxylic acid (4-PhOAPPC) as a white solid (2.53 g, >100 % yield, wet and contaminated

with inorganic salt), which showed a single peak on HPLC and used directly for the next step. MS (electrospray) *m/e* 313 (M+H), Calcd for $C_{18}H_{20}N_2O_3$, 312.

Step 5:



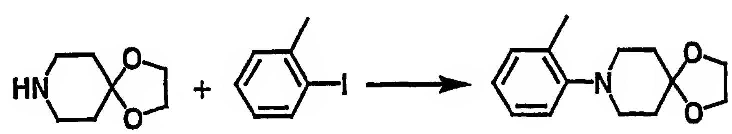
The crude 4-PhOAPPC from the last step was treated with Fmoc-Cl (2.6g, 1.25 equiv) in dioxane (50 L) and aqueous 10 % Na_2CO_3 (50 ml) and stirred vigorously overnight. The reaction mixture was concentrated to remove dioxane, neutralized with 6N HCl to slightly acidic (pH 6) and extracted with EtOAc. The combined organic extracts were washed with brine and dried over Na_2SO_4. Removal of the solvent gave the crude product which was purified on flash chromatography (hexane/EtOAc to CH_2Cl_2/MeOH) to give pure 4-PhOAPPC (2.18 g, 60% overall yield for two steps). ^{1}H NMR (DMSO-d_6): 7.87 (d, 2H), 7.72 (d, 2H), 7.38 (t, 2H), 7.30 (td, 4H), 7.02 (dt, 1H), 6.86-6.96 (m, 6H), 3.35 (m, 2H), 2.94 (t, 2H); MS (electrospray) *m/e* 535 (M+H), Calcd for $C_{33}H_{30}N_2O_5$, 534.

EXAMPLE 22

Preparation of

Fmoc-4-amino-1-(2-methylphenyl)piperidine-4-carboxylic acid(Fmoc-2-MeAppc-OH)

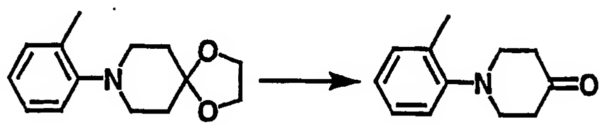
Step 1:



To a solution of 2-iodotoluene (4.36 g, 2.5 mL, 20.0 mmol), 1,4-dioxa-8-azaspiro[4.5]decane (6.88 g, 6.2 mL, 48.1 mmol, 2.4 equiv) and sodium tert-butoxide (5.3 g, 55.2 mmol, 2.8 equiv) in dry dioxane (80 mL) were added tris(dibenzylideneacetone)dipalladium(0) (91 mg,

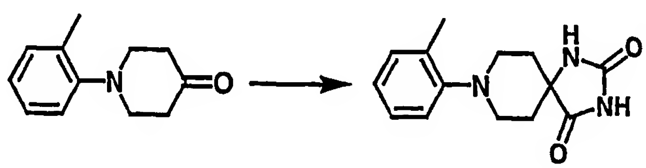
0.1 mmol) and tri-*o*-tolylphosphine (122 mg, 0.4 mmol). The reaction was heated at 90 ^{0}C for 26 hrs. The resulting reaction mixture was concentrated to remove solvent. The residue was treated with water and extracted with EtOAc. The combined organic extracts were combined, washed with brine, dried over Na_2SO_4 and concentrated to give brown oil. This crude product was purified on flash chromatography (hexane/EtOAc, 95/5 to 75/25) to provide the pure product as a slightly yellow solid (2.66 g, 57%). ^{1}H NMR ($CDCl_3$), 7.12-7.18 (m, 2H), 6.94-7.06 (m, 2H), 4.01 (s, 4H), 2.98 (t, 4H) and 1.88 (t, 4H).

Step 2:



To a solution of the ketal (2.66 g, 11.4 mmol) in acetone (70 mL) was added 6N hydrochloric acid (35 mL) and the reaction was heated at 85 °C overnight. The resulting reaction was concentrated to remove solvent. The residue was diluted with EtOAc and neutralized with aqueous NaOH (6N). The layers were separated and the aqueous layer was extracted with EtOAc. The combined organic extracts were washed with brine, dried over Na_2SO_4 and concentrated. The crude product was purified on flash chromatography (hexane/EtOAc, 90/10 to 70/30) to give the product as a yellow oil (2.04 g, 95%). MS (electrospray) *m/e* 190 (M+H), Calcd for $C_{12}H_{15}NO$, 189.

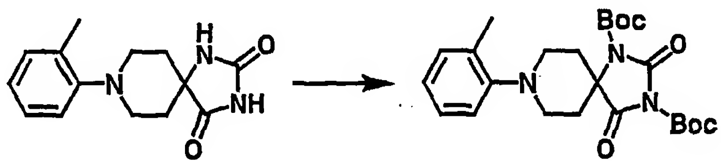
Step 3:



To a solution of the ketone (1.54 g, 8.15 mmol) in ethanol (60 mL) and water (20 mL) in a glass pressure bottle, were added ammonium carbonate (4.69 g, 48.9 mmol, 6 equiv.) and

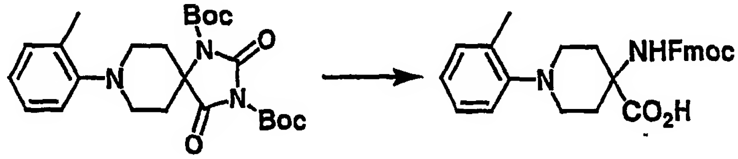
potassium cyanide (800 g, 12.2 mmol, 1.5 equiv.). The mixture was heated at 80-90 ^{0}C for 18 hrs. The cooled reaction mixture was added to icy water (300 ml) and stirred vigorously for 30 min. The resulting precipitate was suction filtered, washed thoroughly with water and dried to yield the hydantoin as a white solid (2.01 g, 95% yield). MS (electrospray) *m/e* 260 (M+H), Calcd for $C_{14}H_{17}N_3O_2$, 259.

Step 4:



To a suspension of the hydantoin (1.07 g, 4.13 mmol) in dry THF (25 mL) were added di-*tert*-butyl dicarbonate (2.25 g, 10.32 mmol, 2.5 equiv), triethylamine (0.63 mL, 460 mg, 4.54 mmol, 1.1 equiv) and DMAP (36 mg, 0.29 mmol) in succession. About 15 minutes after the addition, the reaction turned into a clear yellow solution and was stirred overnight at room temperature. The reaction mixture was concentrated under reduced pressure to yield a solid that was then taken up in EtOAc (300 mL), washed with 1N HCl (3x30 mL), saturated aqueous Na_2CO_3 (2x30 mL) and brine (2x30 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude light yellow product was purified through flash chromatography (hexane/EtOAc, 90/10→80/20) to give the pure bis-Boc hydantoin as a white solid (1.71 g, 90%). MS (electrospray) *m/e* 460 (M+H), Calcd for $C_{24}H_{33}N_3O_6$, 459.

Step 5:



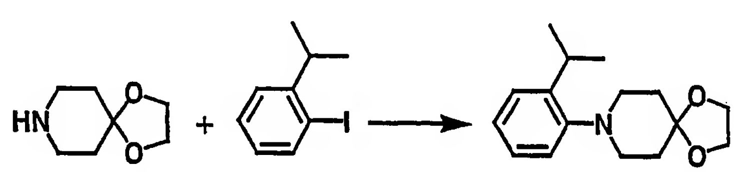
The bis-Boc hydantoin (1.71g, 3.72 mmol) was dissolved in DME (23 mL) to give a clear solution. To this solution was added 1N NaOH (33 mL, 33 mmol) and the reaction was stirred overnight at room temperature, giving a fairly clear mixture. HPLC showed completion of the reaction. The reaction mixture was concentrated under reduced pressure to remove DME and extracted with Et_2O. Without purification, the resulting aqueous layer containing 4-amino-1-(2-methylphenyl)piperidine-4-carboxylic acid (2-MeAPPC) was treated with 6N HCl to adjust the pH to 11-12. This solution (30 mL) was then diluted with 1,4-dioxane (30 mL) and treated with Fmoc-Cl (1.28 g, 4.96 mmol, 1.3 equiv) and stirred overnight at room temperature. The reaction mixture was concentrated under reduced pressure to remove dioxane, neutralized with 1N HCl and extracted with EtOAc. The combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4 and concentrated. The crude product was purified through flash chromatography (hexane/EtOAc→CH_2Cl_2/MeOH) to give the pure product as a white solid (1.09 g, 64 % yield from the bis-Boc hydantoin). ^1H NMR (DMSO-d_6): 7.87 (d, 2H), 7.74 (d, 2H), 7.40 (td, 2H), 7.31 (td, 2H), 7.12 (m, 2H), 6.97 (d, 1H), 6.92 (td, 1H), 2.72-2.88 (m, 4H) and 2.22 (s, 3H); MS (electrospray) *m/e* 457 (M+H), Calcd for $C_{28}H_{28}N_2O_4$, 456.

EXAMPLE 23

Preparation of

Fmoc-4-amino-1-(2-isopropylphenyl)piperidine-4-carboxylic acid (Fmoc-2-iPrAppc-OH)

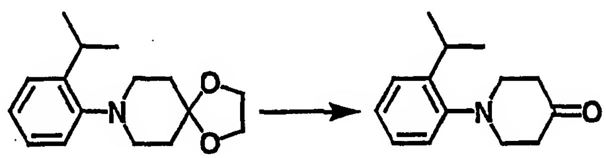
Step 1:



To a solution of 1-iodo-2-*iso*-propylbenzene (10.0 g, 40.7 mmol), 1,4-dioxa-8-azaspiro[4.5]decane (12.0 mL, 13.3 g, 93.0 mmol, 2.3 equiv) and sodium tert-butoxide (10.0 g, 104.2 mmol, 2.6 equiv) in dry dioxane (160 mL) were added tris(dibenzylideneacetone)dipalladium(0) (180 mg, 0.197 mmol) and tri-*o*-tolyl-phosphine

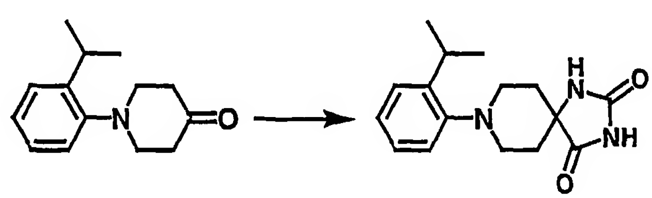
(244 mg, 0.80 mmol) and the reaction was heated at 90 ^{0}C for 26 hrs. The resulting reaction mixture was concentrated to remove solvent, treated with water and extracted with EtOAc. The combined organic extracts were combined, washed with brine, dried over Na_2SO_4 and concentrated to give a brown oil. This crude product was purified on flash chromatography (hexane/EtOAc, 95/5→75/25) to provide the pure product as a slightly yellow solid (3.61 g, 35% yield). MS *m/z* 262 (M+H), Calcd for $C_{16}H_{23}NO_2$, 261.

Step 2:



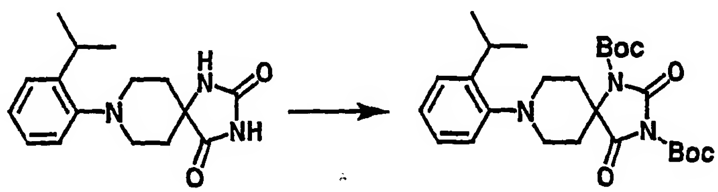
To a solution of the ketal (3.24 g, 12.4 mmol) in acetone (90 mL) was added 6N hydrochloric acid (45 mL) and the reaction was heated at reflux overnight. The resulting reaction mixture was concentrated to remove solvent and the residue was diluted with EtOAc, neutralized with aqueous NaOH (6N). The layers were separated and the aqueous layer was extracted with EtOAc. The combined organic extracts were washed with brine, dried over Na_2SO_4 and concentrated. The crude product was purified on flash chromatography (hexane/EtOAc, 90/10→70/30) to give the product as a yellow oil (2.42 g, 89%). ^{1}H NMR ($CDCl_3$): 7.27 (m, 1H), 7.04-7.19 (m, 3H), 3.58 (m, 1H), 3.20 (t, 4H), 2.60 (t, 4H) and 1.25 (d, 6H); MS *m/z* 218 (M+H), Calcd for $C_{14}H_{19}NO$, 217.

Step 3:



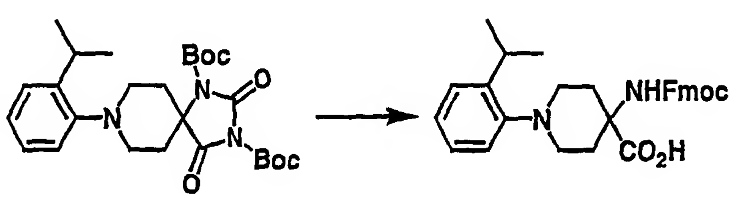
To a solution of the ketone (2.30 g, 10.6 mmol) in ethanol (90 mL) and water (20 mL) in a glass pressure bottle, were added ammonium carbonate (8.1 g, 84.3 mmol, 8 equiv) and potassium cyanide (1.72 g, 26.5 mmol, 2.5 equiv). The mixture was heated at 80-90 ^{0}C for 18 hrs. The cooled reaction mixture was added to icy water (400 ml) and stirred vigorously for 30 min. The resulting precipitate was suction filtered, washed thoroughly with water and dried to yield the hydantoin as a white solid (2.78 g, 91% yield). MS *m/z* 288 (M+H), Calcd for $C_{16}H_{21}N_3O_2$, 287.

Step 4:



To a suspension of the hydantoin (2.74 g, 9.54 mmol) in dry THF (100 mL) were added di-*tert*-butyl dicarbonate (5.2 g, 24.24 mmol, 2.5 equiv), triethylamine (1.5 mL, 1.07 g, 10.5 mmol, 1.1 equiv) and DMAP (46 mg, 0.29 mmol) in succession. About 15 minutes after the addition, the reaction turned into a clear yellow solution and was stirred overnight at room temperature. The reaction mixture was concentrated under reduced pressure to yield a solid that was then taken up in EtOAc (300 mL), washed with brine (3x30 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude light yellow product was purified through flash chromatography (hexane/EtOAc, 90/10→80/20) to give the pure bis-Boc hydantoin as a white solid (4.39 g, 94% yield). MS *m/z* 488 (M+H), Calcd for $C_{26}H_{37}N_3O_6$, 487.

Step 5:



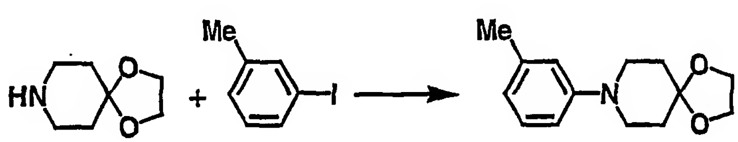
The bis-Boc hydantoin (2.34g, 4.8 mmol) was dissolved in DME (30 mL) to give a clear solution. To this solution was added 1N NaOH (45 mL, 45 mmol) and the reaction was stirred overnight at room temperature, giving a fairly clear mixture. HPLC showed completion of the reaction. The reaction mixture was concentrated under reduced pressure to remove DME and extracted with Et_2O. Without purification, the resulting aqueous layer containing 4-amino-1-(2-isopropylphenyl)piperidine-4-carboxylic acid (2-iPrAPPC) was treated with 6N HCl to adjust the pH to 11-12. This solution (~45 mL) was then diluted with 1,4-dioxane (45 mL) and treated with Fmoc-Cl (1.78 g, 6.89 mmol, 1.5 equiv) and stirred overnight at room temperature. The reaction mixture was concentrated under reduced pressure to remove dioxane, neutralized with 1N HCl and extracted with EtOAc. The combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4 and concentrated. The crude product was purified through flash chromatography (hexane/EtOAc→CH_2Cl_2/MeOH) to give the pure product as a white solid (1.46 g, 63 % yield from the bis-Boc hydantoin). HRMS m/z 507.2263, Calcd for $C_{30}H_{32}N_2O_4Na$, 507.2260.

EXAMPLE 24

Preparation of

Fmoc-4-amino-1-(3-methylphenyl)piperidine-4-carboxylic acid (**Fmoc-3-MeAppc-OH**)

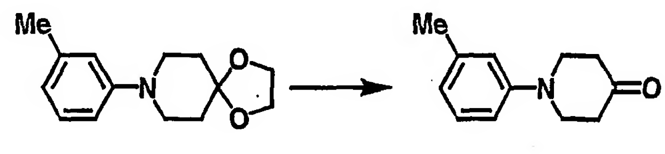
Step 1:



To a solution of 3-iodotoluene (4.36 g, 2.6 mL, 20.0 mmol), 1,4-dioxa-8-azaspiro [4.5] decane (6.88 g, 6.2 mL, 48.1 mmol, 2.4 equiv) and sodium tert-butoxide (5.3 g, 55.2 mmol, 2.8 equiv) in dry dioxane (80 mL) were added tris (dibenzylideneacetone) dipalladium (0) (91 mg, 0.1 mmol) and tri-*o*-tolylphosphine (122 mg, 0.4 mmol). The reaction was heated at 90 ^{0}C for 26 hrs. The resulting reaction mixture was concentrated to remove solvent. The

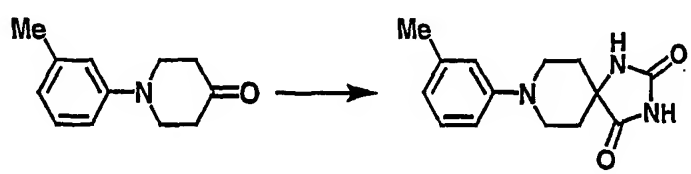
residue was treated with water and extracted with EtOAc. The combined organic extracts were combined, washed with brine, dried over Na_2SO_4 and concentrated to give a brown oil. This crude product was purified on flash chromatography (hexane/EtOAc, 95/5 to 75/25) to provide the pure product as a slightly yellow solid (3.21 g, 69%).

Step 2:



To a solution of the ketal (1.25 g, 5.36 mmol) in acetone (20 mL) was added 6N hydrochloric acid (10 mL) and the reaction was heated at reflux overnight. The resulting reaction was concentrated to remove solvent. The residue was diluted with EtOAc and neutralized with aqueous NaOH (6N). The layers were separated and the aqueous layer was extracted with EtOAc. The combined organic extracts were washed with brine, dried over Na_2SO_4 and concentrated. The crude product was purified on flash chromatography (hexane/EtOAc, 90/10 to 70/30) to give the product as a yellow oil (843 mg, 83% yield). MS *m/z* 190 (M+H), Calcd for $C_{12}H_{15}NO$, 189.

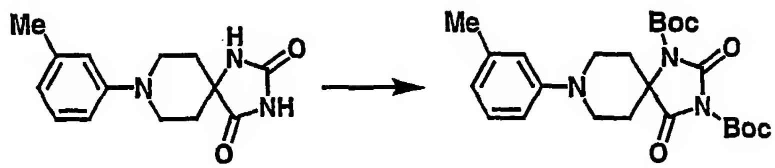
Step 3:



To a solution of the ketone (763 g, 4.03 mmol) in ethanol (45 mL) and water (15 mL) in a glass pressure bottle, were added ammonium carbonate (3.09 g, 32.21 mmol, 8 equiv) and potassium cyanide (675 mg, 10.38 mmol, 2.5 equiv). The mixture was heated at 80-90 ^{0}C for 18 hrs. The cooled reaction mixture was added to icy water (200 ml) and stirred vigorously for 30 min. The resulting precipitate was suction filtered, washed thoroughly with water and

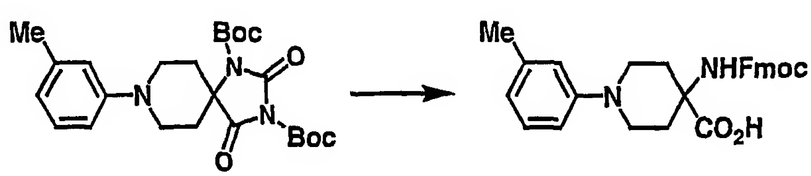
dried to yield the hydantoin as a white solid (930 mg, 89% yield). MS *m/z* 260 (M+H), Calcd for $C_{14}H_{17}N_3O_2$, 259.

Step 4:



To a suspension of the hydantoin (780 mg, 3.012 mmol) in dry THF (22 mL) were added di-*tert*-butyl dicarbonate (1.64 g, 7.52 mmol, 2.5 equiv), triethylamine (0.42 mL, 305 mg, 3.01 mmol, 1.0 equiv) and DMAP (20 mg, 0.164 mmol) in succession. About 5 minutes after the addition, the reaction turned into a clear yellow solution and was stirred overnight at room temperature. The reaction mixture was concentrated under reduced pressure to yield a solid that was then taken up in EtOAc (300 mL), washed with brine (3x30 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude light yellow product was purified through flash chromatography (hexane/EtOAc, 90/10→80/20) to give the pure bis-Boc hydantoin as a white solid (1.37 g, quantitative). HRMS m/z 482.2261 (M+Na), Calcd. for $C_{24}H_{33}N_3O_6Na$, 482.2267.

Step 5:



The bis-Boc hydantoin (1.29 g, 2.818 mmol) was dissolved in DME (20 mL) to give a clear solution. To this solution was added 1N NaOH (25 mL, 25 mmol) and the reaction was stirred overnight at room temperature, giving a fairly clear mixture. HPLC showed completion of the reaction. The reaction mixture was concentrated under reduced pressure to

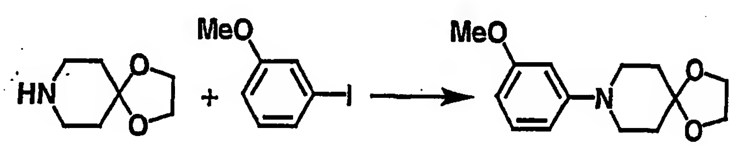
remove DME and extracted with Et_2O. Without purification, the resulting aqueous layer containing 4-amino-1-(3-methylphenyl)piperidine-4-carboxylic acid (3-MeAPPC) was treated with 6N HCl to adjust the pH to 11-12. This solution (30 mL) was then diluted with 1,4-dioxane (30 mL) and treated with Fmoc-Cl (1.46 mg, 5.65 mmol, 2.0 equiv) and stirred overnight at room temperature. The reaction mixture was concentrated under reduced pressure to remove dioxane, neutralized with 1N HCl and extracted with EtOAc. The combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4 and concentrated. The crude product was purified through flash chromatography (hexane/EtOAc→ CH_2Cl_2/MeOH) to give the pure product as a white solid (1.002 g, 78 % yield from the bis-Boc hydantoin). HRMS m/z 479.1940 (M+Na), Calcd. for $C_{28}H_{28}N_2O_4Na$, 479.1947.

EXAMPLE 25

Preparation of

Fmoc-4-amino-1-(3-methoxyphenyl)piperidine-4-carboxylic acid **(Fmoc-3-MeOAppc-OH)**

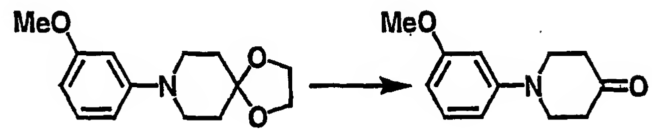
Step 1:



To a solution of 3-iodoanisole (4.68 g, 2.4 mL, 20.0 mmol), 1,4-dioxa-8-azaspiro [4.5] decane (6.2 mL, 6.88 g, 48.1 mmol, 2.4 equiv) and sodium tert-butoxide (5.3 g, 55.2 mmol, 2.8 equiv) in dry dioxane (80 mL) were added tris(dibenzylideneacetone)dipalladium(0) (91 mg, 0.1 mmol) and tri-*o*-tolylphosphine (122 mg, 0.4 mmol) and the reaction was heated at 90 ^{0}C for 26 hrs. The resulting reaction mixture was concentrated to remove solvent and the residue was treated with water and extracted with EtOAc. The combined organic extracts were combined, washed with brine, dried over Na_2SO_4 and concentrated to give brown oil. This crude product was purified on flash chromatography (hexane/EtOAc, 95/5 to 75/25) to

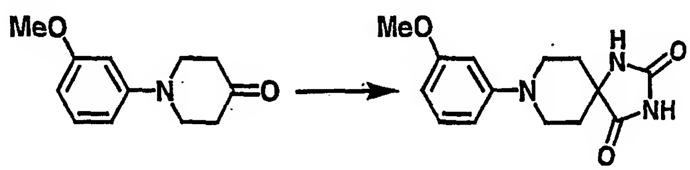
provide the pure product as a slightly yellow solid (3.10 g, 62% yield). MS *m/z* (M+H), 250 (M+H), Calcd for $C_{14}H_{19}NO_3$, 249.

Step 2:



To a solution of the ketal (3.10 g, 12.45 mmol) in acetone (90 mL) was added 6N hydrochloric acid (45 mL) and the reaction was heated at reflux overnight. The resulting reaction was concentrated to remove solvent. The residue was diluted with EtOAc and neutralized with aqueous NaOH (6N). The layers were separated and the aqueous layer was extracted with EtOAc. The combined organic extracts were washed with brine, dried over Na_2SO_4 and concentrated. The crude product was purified on flash chromatography (hexane/EtOAc, 90/10 to 70/30) to give the product as a yellow oil (2.53 g, 99% yield). ^{1}H NMR ($CDCl_3$): 7.20 (m, 1H), 6.58 (d, 1H), 6.39-6.56 (m, 2H), 3.80 (s, 3H), 3.59 (m, 4H) and 2.58 (m, 4H).

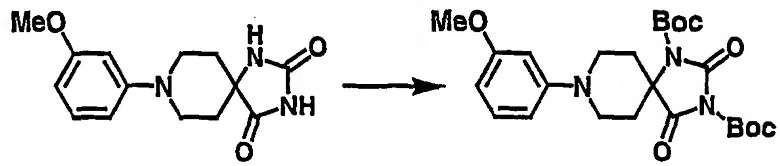
Step 3:



To a solution of the ketone (1.81 g, 8.82 mmol) in ethanol (60 mL) and water (20 mL) in a glass pressure bottle, were added ammonium carbonate (6.77 g, 70.52 mmol, 8 equiv) and potassium cyanide (1.14g, 17.6 mmol, 2.0 equiv). The mixture was heated at 80-90 ^{0}C for 18 hrs. The cooled reaction mixture was added to icy water (200 ml) and stirred vigorously for 30 min. The resulting precipitate was suction filtered, washed thoroughly with water and

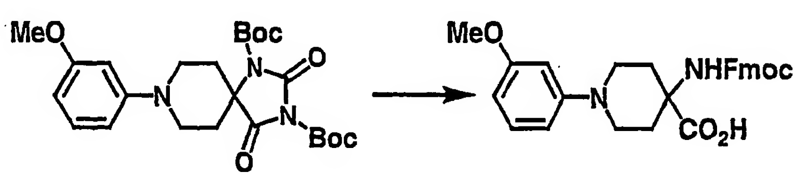
dried to yield the hydantoin as a white solid (2.23 g, 92% yield). MS *m/z* 276 (M+H), Calcd for $C_{14}H_{17}N_3O_3$, 275.

Step 4:



To a suspension of the hydantoin (1.10 g, 4.00 mmol) in dry THF (50 mL) were added di-*tert*-butyl dicarbonate (2.18 g, 10.0 mmol, 2.5 equiv), triethylamine (0.62 mL, 445 mg, 4.4 mmol, 1.1 equiv) and DMAP (20 mg, 0.164 mmol) in succession. About 15 minutes after the addition, the reaction turned into a clear yellow solution and was stirred overnight at room temperature. The reaction mixture was concentrated under reduced pressure to yield a solid that was then taken up in EtOAc (300 mL), washed with brine (3x30 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude light yellow product was purified through flash chromatography (hexane/EtOAc, 90/10→80/20) to give the pure bis-Boc hydantoin as a white solid (1.90 g, quantitative). ^1H NMR ($CDCl_3$): 7.16 (t, 1H), 6.57 (d, 1H), 6.24 (s, 1H), 6. 19 (d, 1H), 3.77 (s, 3H), 1.58 (s, 9H), 1.42 (s, 9H); MS *m/z* 476 (M+H), Calcd for $C_{24}H_{33}N_3O_7$, 475.

Step 5:



The bis-Boc hydantoin (1.06 g, 2.23 mmol) was dissolved in DME (20 mL) to give a clear solution. To this solution was added 1N NaOH (20 mL, 20 mmol) and the reaction was stirred overnight at room temperature, giving a fairly clear mixture. HPLC showed

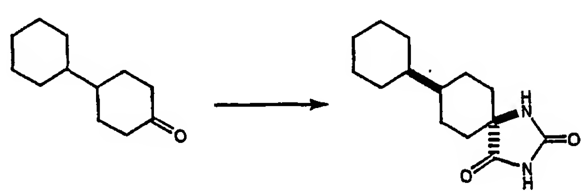
completion of the reaction. The reaction mixture was concentrated under reduced pressure to remove DME and extracted with Et_2O. Without purification, the resulting aqueous layer containing 4-amino-1-(3-methoxyphenyl)piperidine-4-carboxylic acid (3-MeOAPPC) was treated with 6N HCl to adjust the pH to 11-12. This solution (35 mL) was then diluted with 1,4-dioxane (35 mL) and treated with Fmoc-Cl (755 mg, 2.93 mmol, 1.3 equiv) and stirred overnight at room temperature. The reaction mixture was concentrated under reduced pressure to remove dioxane, neutralized with 1N HCl and extracted with EtOAc. The combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4 and concentrated. The crude product was purified through flash chromatography (hexane/EtOAc→ CH_2Cl_2/MeOH) to give the pure product as a white solid (668 mg, 63 % yield from the bis-Boc hydantoin). ^{1}H NMR ($CDCl_3$): 7.83 (d, 2H), 7.72 (d, 2H), 7.41 (td, 2H), 7.34 (dt, 2H), 7.16 (t, 1H), 6.52 (d, 1H), 6.42 (s, 1H), 6.36 (d, 1H), 4.25 (m, 3H), 3.68 (s, 3H), 3.23-3.40 (m, 2H), 2.96 (t, 2H) and 1.86-2.18 (m, 4H). HRMS m/z 495.1901 (M+Na), Calcd. for $C_{28}H_{28}N_2O_5Na$, 495.1896.

EXAMPLE 26

Preparation of

Fmoc-1-amino-4-cyclohexylcyclohexane-1-carboxylic acid (**Fmoc-Achc-OH**)

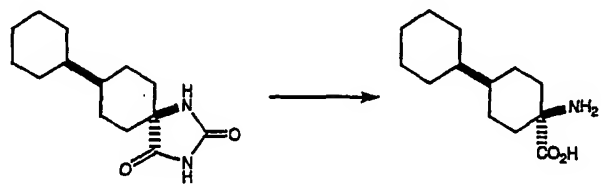
Step 1:



A mixture of 4-cyclohexylcyclohexanone (3.00 g, 16.6 mmole), potassium cyanide (1.63 g, 25.0 mmole), ammonium carbonate (9.59 g, 99.8 mmole), ethanol (75 ml) and water (15 ml) in a sealed, thick walled pressure flask was heated in a 80°C oil bath for 15 hours. After cooling to room temperature, the white slurry was poured into ice-water and stirred at room temperature for a couple of hours. Filtration and air-drying gave hydantoin (6.10 g, still wet,

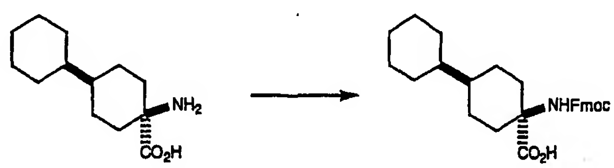
>100% yield) as a white solid. ^{1}H NMR (DMSO-d_6) δ 10.52 (1H, broad, NH), 8.43 (1H, broad s, NH), 0.80-1.80 (20H, m). LRMS (APCI): $C_{14}H_{22}N_2O_2$, calc. 250; observed: 249 (M-H), 251 (M+H).

Step 2:



A mixture of hydantoin (1.39 g, 5.55 mmole) and 6N sodium hydroxide solution (50 ml) in a sealed, thick walled pressure flask was heated in a 130°C oil bath for 2 days. The reaction mixture was cooled in an ice bath, neutralized to ~ pH 7 using concentrated hydrochloric acid. The white slurry was filtered and the precipitates rinsed with water to give crude 1-amino-4-cyclohexylcyclohexane-1-carboxylic acid (48.3 g, wet and containing inorganic salts, >100% yield). LRMS (Electrospray): $C_{13}H_{23}NO_2$, calc. 225; observed: 226 (M+H).

Step 3:



A mixture of crude 1-amino-4-cyclohexylcyclohexane-1-carboxylic acid (48.3 g, 5.55 mmole theoretical), triethylamine (1.0 ml, 7.17 mmole), 9-fluorenylmethyl succinimidyl carbonate (Fmoc-OSu, 2.43 g, 7.20 mmole) in acetonitrile (75 ml) and water (75 ml) was stirred at room temperature for 24 hours. The reaction mixture was concentrated in vacuo to remove most of the acetonitrile, acidified to pH ~3 with 10% aqueous citric acid solution, and the white emulsion extracted three times with methylene chloride. The combined organic layers were washed with water, brine, dried over magnesium sulfate. Filtration and concentration

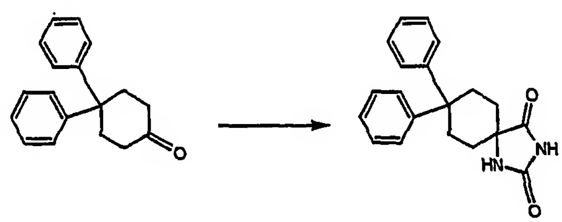
gave a crude oil which was purified by column chromatography (eluted with 1 → 5 → 8% methanol/methylene chloride) to give Fmoc-1-amino-4-*trans*-cyclohexylcyclohexane-1-carboxylic acid (250 mg, 10% yield for two steps). HRMS (FAB): $C_{28}H_{34}NO_4$ (M+H) calc. 448.2488; observed: 448.2497.

EXAMPLE 27

Preparation of

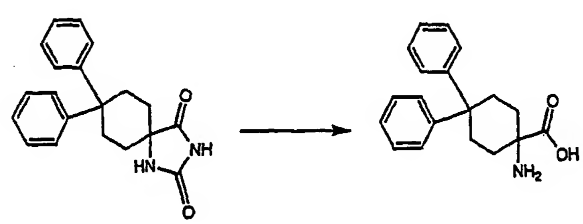
Fmoc-1-amino-4,4-diphenylcyclohexane-1-carboxylic acid (Fmoc-Adpc-OH)

Step 1:



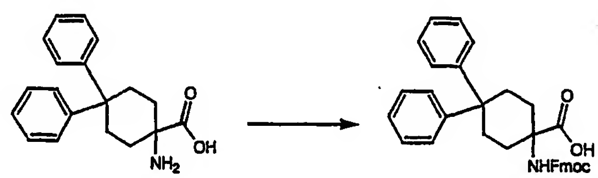
A mixture of 4,4-diphenylcyclohexanone (prepared by hydrogenation of 4,4-diphenylcyclohexenone according to the procedures of Freeman, P.K. *et.al. J. Org. Chem.* **1989**, *54*, 782-789) (1.55 g, 6.19 mmole), potassium cyanide (0.65 g, 9.97 mmole), ammonium carbonate (3.60 g, 37.5 mmole), ethanol (48 ml) and water (12 ml) in a sealed, thick walled pressure flask was heated in a 80°C oil bath for 24 hours. After cooling to room temperature, the white slurry was poured into ice-water and stirred at room temperature for a couple of hours. Filtration and air-drying gave hydantoin (1.89 g, 95% yield) as a white solid. ^{1}H NMR (DMSO-d_6) δ 10.57 (1H, broad, NH), 8.59 (1H, broad s, NH), 7.00-7.50 (10H, m, phenyl). LRMS (Electrospray): $C_{20}H_{20}N_2O_2$, calc. 320; observed: 319 (M-H).

Step 2:



A mixture of hydantoin (1.88 g, 5.87 mmole), barium hydroxide monohydrate (5.60 g, 29.6 mmole) and water (100 ml, too dilute!) in a sealed, thick walled pressure flask was heated in a 105°C oil bath for 2 days. More barium hydroxide monohydrate (5.60 g, 29.6 mmole) was added and the mixture was heated in a 105°C oil bath for another 24 hours. The reaction mixture was cooled to room temperature, acidified to ~ pH 3 using 4N sulfuric acid while being stirred vigorously. The suspension was stirred in a boiling water bath for two hours and cooled to room temperature. The white suspension was filtered and the precipitates rinsed with water. The combined filtrate and washings were concentrated in vacuo to ~ 30 ml. Neutralization with concentrated ammonium hydroxide solution gave white precipitates which were filtered, washed with water and dried in vacuo overnight to give crude 1-amino-4,4-diphenylcyclohexane-1-carboxylic acid (0.52 g, 30% yield) as a white solid. LRMS (Electrospray): $C_{19}H_{21}NO_2$, calc. 295; observed: 294 (M-H), 296 (M+H).

Step 3:



A mixture of crude 1-amino-4,4-diphenylcyclohexane-1-carboxylic acid (510 mg, 1.73 mmole), triethylamine (0.37 ml, 2.65 mmole), 9-fluorenylmethyl succinimidyl carbonate (Fmoc-OSu, 880 mg, 2.61 mmole) in acetonitrile (25 ml) and water (25 ml) was stirred at room temperature overnight. TLC analysis of the reaction indicated the presence of starting material amino acid. 9-fluorenylmethyl succinimidyl carbonate (200 mg) and acetonitrile (5 ml) were added and the mixture was stirred at room temperature for another 24 hours. The reaction mixture was concentrated in vacuo to remove most of the acetonitrile, acidified to pH ~3 with 10% aqueous citric acid solution, and the white emulsion extracted three times with ethyl acetate. The combined organic layers were washed with water, brine, dried over sodium sulfate. Filtration and concentration gave a crude oil which was purified by column chromatography (eluted with 1 → 4 → 8% methanol/methylene chloride) to give Fmoc-1-

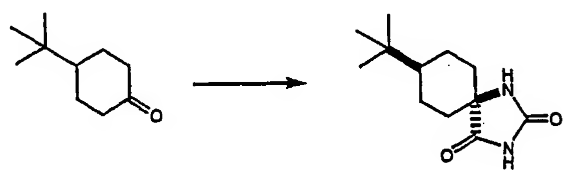
amino-4,4-diphenylcyclohexane-1-carboxylic acid (350 mg, 39% yield) as a white solid. HRMS (FAB): $C_{34}H_{32}NO_4$ (M+H) calc. 518.2331; observed: 518.231

EXAMPLE 28

Preparation of

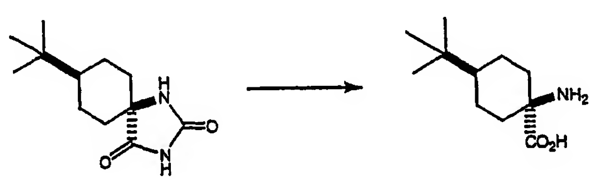
Fmoc-1-amino-4-*trans*-*t*-butylcyclohexane-1-carboxylic acid (Fmoc-Abc-OH)

Step 1:



A mixture of 4-*t*-butylcyclohexanone (2.00 g, 13.0 mmole), potassium cyanide (1.27 g, 19.5 mmole), ammonium carbonate (7.48 g, 77.8 mmole), ethanol (60 ml) and water (12 ml) in a sealed, thick walled pressure flask was heated in a 80°C oil bath for 15 hours. After cooling to room temperature, the white slurry was poured into ice-water and stirred at room temperature for a couple of hours. Filtration gave hydantoin (2.78 g, 96% yield) as a white solid which was used in the next step as a crude. ^{1}H NMR (DMSO-d_6) δ 10.52 (1H, broad, NH), 8.50 (1H, broad s, NH), 0.81 (9H, s, *t*-Bu).

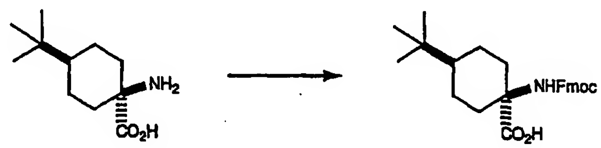
Step 2:



A mixture of hydantoin (2.78 g, 12.4 mmole), barium hydroxide monohydrate (11.74 g, 62.0 mmole) and water (50 ml) in a sealed, thick walled pressure flask was heated in a 120°C oil bath for 2 days. The reaction mixture was cooled to room temperature, acidified to ~ pH 3 using 4N sulfuric acid while being stirred vigorously. The suspension was stirred in a boiling

water bath for one hour and cooled to room temperature. The white suspension was filtered and the precipitates rinsed with water. The combined filtrate and washings were concentrated in vacuo to ~ 30 ml. Neutralization with concentrated ammonium hydroxide solution gave white precipitates which were filtered, washed with water and dried in vacuo overnight to give 1-amino-4-*trans*-*t*-butylcyclohexane-1-carboxylic acid (2.10 g, 85% yield) as a white solid.

Step 3:



A mixture of crude 1-amino-4-*trans*-*t*-butylcyclohexyl-1-carboxylic acid (2.10 g, 10.54 mmole), 9-fluorenylmethyl succinimidyl carbonate (Fmoc-OSu, 6.33 g, 7.20 mmole) in dioxane (150 ml) and 10% sodium carbonate solution (120 ml) was stirred at room temperature for 24 hours. The reaction mixture was concentrated in vacuo to remove most of the dioxane, acidified to pH ~3 with 3N HCl, and the white emulsion extracted twice with methylene chloride. The combined organic layers were washed with water, brine, dried over magnesium sulfate. Filtration and concentration gave a crude which was purified by column chromatography (eluted with 1 → 4 → 5% methanol/methylene chloride) to give Fmoc-1-amino-4-*trans*-*t*-butylcyclohexane-1-carboxylic acid (1.42 g, 32% yield). HRMS (FAB): $C_{26}H_{32}NO_4$ (M+H) calc. 422.2331; observed: 422.23

EXAMPLE 29

Preparation of

Fmoc-Linker-BHA Resin

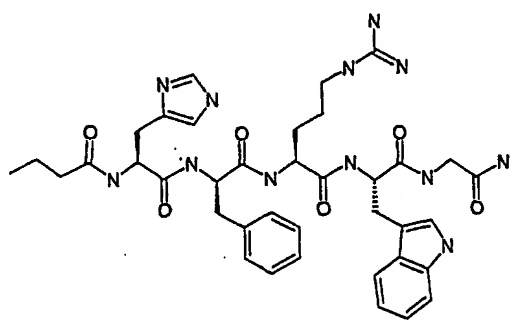
Benzhydrylamine copolystyrene-1% divinylbenzene cross-linked resin (10.0 g, 9.3 mequiv, 100-200 ASTM mesh, Advanced ChemTech) was swelled in 100 mL CH_2Cl_2, filtered and washed successively with 100 ml each of CH_2Cl_2, 6% DIPEA/CH_2Cl_2 (two

times), CH_2Cl_2 (two times). The resin was treated with p- [(R, S)-α-[1-(9H-fluoren-9-yl)-methoxyformamido]-2,4-dimethoxybenzyl]-phenoxyacetic acid (Fmoc-Linker) (7.01 g, 13.0 mmole), N-hydroxybenzotriazole (2.16 g, 16.0 mmole), and diisopropylcarbodiimide (2.04 ml, 13.0 mmol) in 100 mL 25% DMF/CH_2Cl_2 for 24 hours at room temperature. The resin was filtered and washed successively with 100 ml each of CH_2Cl_2 (two times), isopropanol (two times), DMF, and CH_2Cl_2 (three times). A Kaiser ninhydrin analysis was negative. The resin was dried under vacuum to yield 16.12 g of Fmoc-Linker-BHA resin. A portion of this resin (3.5 mg) was subjected to Fmoc deprotection and quantitative UV analysis indicated a loading of 0.56 mmol/g.

EXAMPLE 30

Preparation of

Bu-His-(D)Phe-Arg-Trp-Gly-NH_2



Fmoc-Linker-BHA resin (360 mg, 0.2 mmol) from Example 29 were subjected to solid phase synthesis using protocol 1 described above. All couplings were performed using HBTU in DMF as the coupling agent and DIPEA (3 equiv.) as base. Five coupling cycles were performed of one cycle each with Fmoc-Gly (180 mg, 0.6 mmol) and HBTU (226 mg, 0.6 mmol), Fmoc-Trp (260 mg, 0.6 mmol) and HBTU (226 mg, 0.6 mmol), Fmoc-Arg (Pmc) (400 mg, 0.6 mmol) and HBTU (226 mg, 0.6 mmol), Fmoc-(D)Phe (240 mg, 0.6 mmol) and HBTU (226 mg, 0.6 mmol), **Fmoc-His (Trt)** (300 mg 0.6 mmol) and HBTU (226 mg, 0.6 mmol). The peptide resin was carried through steps 1 - 5 of protocol 1, washed with CH_2Cl_2 (three times) and treated with 1 mL butyric anhydride in 6% DIPEA/CH_2Cl_2 30 minutes.

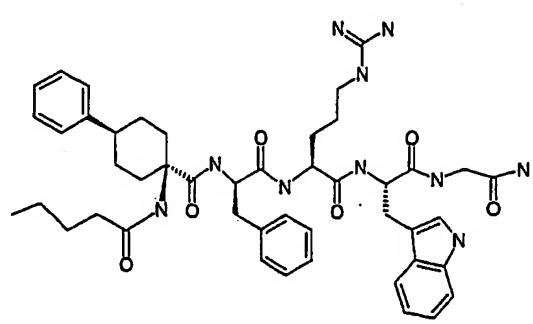
The resin was filtered and washed successively with 20 ml each of CH_2Cl_2 (two times), isopropanol, and CH_2Cl_2 (three times). The resin was dried under vacuum to yield 600 mg of Bu-Pentapeptide resin.

The Bu-Pentapeptide resin was treated with 40 µL ethanedithiol, 40 µL dimethylsulfide, 120 µL anisole, and 4 mL trifluoroacetic acid at room temperature for 180 min. The resin was filtered off, washed with ~2 ml TFA and the filtrates precipitated in chilled ethyl ether. The precipitates were centrifuged and the ether layer decanted. The residue was washed with two or three volumes of Et_2O and recentrifuged and the crude product was dried under vacuum to yield 130 mg of an off-white solid.

This crude material was purified by preparative HPLC on a Vydac C18-column (2.5 x 20 cm) and eluted with a linear gradient of 10-60% B (buffer A: 0.1% TFA/H_2O, buffer B: 0.1% TFA/CH_3CN) in 60 min., flow rate 8ml/min, detection 280 nm. The main peak was cut by analytical HPLC analysis of collected fractions, pooled and lyophilized to yield 52 mg (34 %) of a white, amorphous powder. This compound was homogeneous by HPLC. LR-Electrospray $C_{38}H_{50}N_{12}O_6$ cal: 770 observed: m/z (771 M+H).

EXAMPLE 31

Penta-Apc-(D)Phe-Arg-Trp-Gly-NH_2



Fmoc-Linker-BHA resin (360 mg, 0.2 mmol) from Example 29 were subjected to solid phase synthesis using protocol 1 described above. All couplings were performed using HBTU in

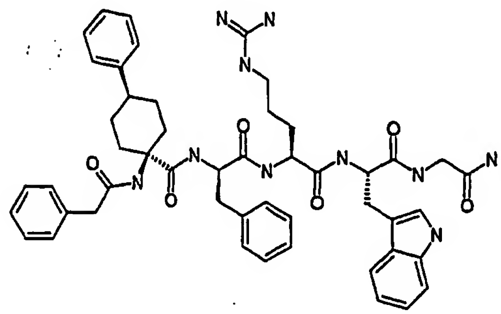
DMF as the coupling agent and DIPEA (3 equiv.) as base. Five coupling cycles were performed of one cycle each with Fmoc-Gly (180 mg, 0.6 mmol) and HBTU (226 mg, 0.6 mmol), Fmoc-Trp (260 mg, 0.6 mmol) and HBTU (226 mg, 0.6 mmol), Fmoc-Arg (Pmc) (400 mg, 0.6 mmol) and HBTU (226 mg, 0.6 mmol), Fmoc-(D)Phe (240 mg, 0.6 mmol) and HBTU (226 mg, 0.6 mmol), **Fmoc-Apc** (275 mg 0.6 mmol) and HBTU (226 mg, 0.6 mmol). The peptide resin was carried through steps 1 - 5 of protocol 1, washed with CH_2Cl_2 (three times) and treated with 1 mL valeric anhydride in 6% DIPEA/CH_2Cl_2 30 minutes. The resin was filtered and washed successively with 20 ml each of CH_2Cl_2 (two times), isopropanol, and CH_2Cl_2 (three times). The resin was dried under vacuum to yield 580 mg of Pentyl-Pentapeptide resin.

The Pentyl-Pentapeptide resin was treated with 40 μL ethanedithiol, 40 μL dimethylsulfide, 120 μL anisole, and 4 mL trifluoroacetic acid at room temperature for 180 min. The resin was filtered off, washed with ~2 ml TFA and the filtrates precipitated in chilled ethyl ether. The precipitates were centrifuged and the ether layer decanted. The residue was washed with two or three volumes of Et_2O and recentrifuged and the crude product was dried under vacuum to yield 145 mg of an off-white solid.

This crude material was purified by preparative HPLC on a Vydac C18-column (2.5 x 20 cm) and eluted with a linear gradient of 10-60% B (buffer A: 0.1% TFA/H_2O, buffer B: 0.1% TFA/CH_3CN) in 60 min., flow rate 8ml/min, detection 280 nm. The main peak was cut by analytical HPLC analysis of collected fractions, pooled and lyophilized to yield 61 mg (36 %) of a white, amorphous powder. This compound was homogeneous by HPLC. LR-Electrospray: $C_{46}H_{60}N_{10}O_6$, cal: 849 observed: m/z (850 M+H).

EXAMPLE 32

Phenylacetyl-Apc-(D)Phe-Arg-Trp-Gly-NH$_2$



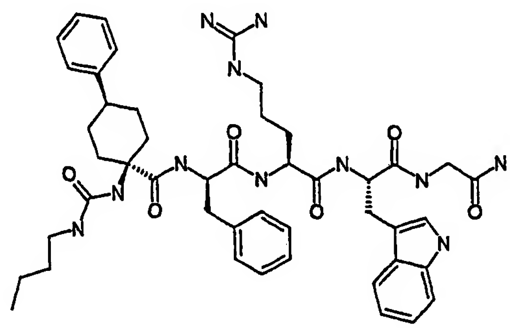
Fmoc-Linker-BHA resin (360 mg, 0.2 mmol) from Example 29 were subjected to solid phase synthesis using protocol 1 described above. All couplings were performed using HBTU in DMF as the coupling agent and DIPEA (3 equiv.) as base. Five coupling cycles were performed of one cycle each with Fmoc-Gly (180 mg, 0.6 mmol) and HBTU (226 mg, 0.6 mmol), Fmoc-Trp (260 mg, 0.6 mmol) and HBTU (226 mg, 0.6 mmol), Fmoc-Arg (Pmc) (400 mg, 0.6 mmol) and HBTU (226 mg, 0.6 mmol), Fmoc-(D)Phe (240 mg, 0.6 mmol) and HBTU (226 mg, 0.6 mmol), **Fmoc-Apc** (275 mg 0.6 mmol) and HBTU (226 mg, 0.6 mmol). The peptide resin was carried through steps 1 - 5 of protocol 1, washed with CH_2Cl_2 (three times) and treated with phenylacetic acid (82 mg, 0.6 mmole) and HBTU (226 mg, 0.6 mmol) in DMF. The resin was filtered and washed successively with 20 ml each of CH_2Cl_2 (two times), isopropanol, and CH_2Cl_2 (three times). The resin was dried under vacuum to yield 620 mg of Phenylacetyl-Pentapeptide resin.

The Phenylacetyl-Pentapeptide resin was treated with 40 µL ethanedithiol, 40 µL dimethylsulfide, 120 µL anisole, and 4 mL trifluoroacetic acid at room temperature for 180 min. The resin was filtered off, washed with ~2 ml TFA and the filtrates precipitated in chilled ethyl ether. The precipitates were centrifuged and the ether layer decanted. The residue was washed with two or three volumes of Et_2O and recentrifuged and the crude product was dried under vacuum to yield 155 mg of an off-white solid.

This crude material was purified by preparative HPLC on a Vydac C18-column (2.5 x 20 cm) and eluted with a linear gradient of 10-60% B (buffer A: 0.1% TFA/H_2O, buffer B: 0.1% TFA/CH_3CN) in 60 min., flow rate 8ml/min, detection 280 nm. The main peak was cut by analytical HPLC analysis of collected fractions, pooled and lyophilized to yield 55 mg (31 %) of a white, amorphous powder. This compound was homogeneous by HPLC. LR-Electrospray: $C_{49}H_{58}N_{10}O_6$, cal: 883 observed: m/z (884 M+H).

EXAMPLE 33

Bu-Carbamoyl-Apc-(D)Phe-Arg-Trp-Gly-NH_2



Fmoc-Linker-BHA resin (360 mg, 0.2 mmol) from Example 29 were subjected to solid phase synthesis using protocol 1 described above. All couplings were performed using HBTU in DMF as the coupling agent and DIPEA (3 equiv.) as base. Five coupling cycles were performed of one cycle each with Fmoc-Gly (180 mg, 0.6 mal) and HBTU (226 mg, 0.6 mal), Fmoc-Trp (260 mg, 0.6 mmol) and HBTU (226 mg, 0.6 mmol), Fmoc-Arg (Pmc) (400 mg, 0.6 mmol) and HBTU (226 mg, 0.6 mmol), Fmoc-(D)Phe (240 mg, 0.6 mmol) and HBTU (226 mg, 0.6 mmol), **Fmoc-Apc** (275 mg 0.6 mmol) and HBTU (226 mg, 0.6 mmol). The peptide resin was carried through steps 1 - 5 of protocol 1, washed with CH_2Cl_2 (three times) and treated n-butyl isocyante (5 eq) in 6% DIPEA/DMF for 12 hours.. The resin was filtered and washed successively with 20 ml each of CH_2Cl_2 (two times), isopropanol, and CH_2Cl_2 (three times). The resin was dried under vacuum to yield 550 mg of Butyl urea-Pentapeptide resin.

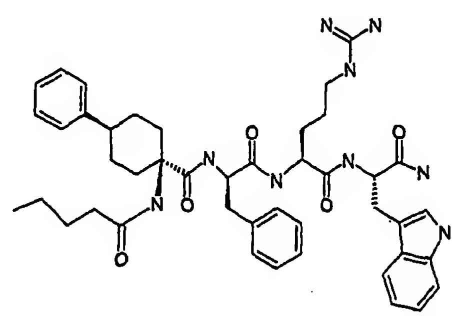
The Butyl urea-Pentapeptide resin was treated with 40 µL ethanedithiol, 40 µL dimethylsulfide, 120 µL anisole, and 4 mL trifluoroacetic acid at room temperature for 180 min. The resin was filtered off, washed with ~2 ml TFA and the filtrates precipitated in chilled ethyl ether. The precipitates were centrifuged and the ether layer decanted. The residue was washed with two or three volumes of Et_2O and recentrifuged and the crude product was dried under vacuum to yield 135 mg of an off-white solid.

This crude material was purified by preparative HPLC on a Vydac C18-column (2.5 x 20 cm) and eluted with a linear gradient of 10-60% B (buffer A: 0.1% TFA/H_2O, buffer B: 0.1% TFA/CH_3CN) in 60 min., flow rate 8ml/min, detection 280 nm. The main peak was cut by analytical HPLC analysis of collected fractions, pooled and lyophilized to yield 55 mg (31 %) of a white, amorphous powder. This compound was homogeneous by HPLC. LR-Electrospray: $C_{46}H_{61}N_{11}O_6$, cal: 864 observed: m/z (865 M+H).

EXAMPLE 34

Preparation of

Penta-Apc-(D)Phe-Arg-Trp-NH_2



Fmoc-Linker-BHA resin (360 mg, 0.2 mmol) from Example 29 were subjected to solid phase synthesis using Protocol 1 above. All couplings were performed using HBTU in DMF as the coupling agent and DIPEA (3 equiv.) as base. Four coupling cycles were performed of one cycle each with), Fmoc-Trp (260 mg, 0.6 mmol) and HBTU (226 mg, 0.6 mmol), Fmoc-Arg (Pmc) (400 mg, 0.6 mmol) and HBTU (226 mg, 0.6 mmol), Fmoc-(D)Phe (240 mg, 0.6

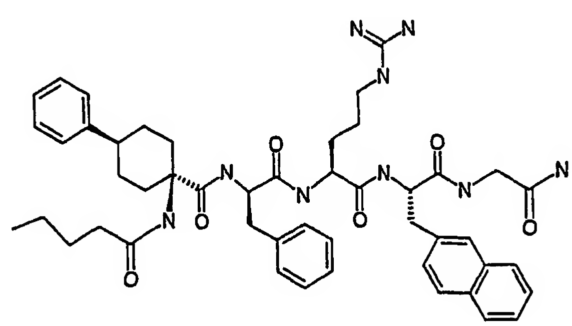
mmol) and HBTU (226 mg, 0.6 mmol), **Fmoc-Apc** (275 mg 0.6 mmol) and HBTU (226 mg, 0.6 mmol). The peptide resin was carried through steps 1 - 5 of protocol 1, washed with CH_2Cl_2 (three times) and treated with 1 mL valeric anhydride in 6% DIPEA/CH_2Cl_2 30 minutes. The resin was filtered and washed successively with 20 ml each of CH_2Cl_2 (two times), isopropanol, and CH_2Cl_2 (three times). The resin was dried under vacuum to yield 600 mg of pentyl-tetrapeptide resin.

The Pentyl-tetra peptide resin was treated with, 40 µL dimethylsulfide, 120 µL anisole, and 4 mL trifluoroacetic acid at room temperature for 180 min. The resin was filtered off, washed with ~2 ml TFA and the filtrates precipitated in chilled ethyl ether. The precipitates were centrifuged and the ether layer decanted. The residue was washed with two or three volumes of Et_2O and recentrifuged and the crude product was dried under vacuum to yield 110 mg of an off-white solid.

This material was purified by preparative HPLC on a Vydac C18-column (2.5 x 20 cm) and eluted with a linear gradient of 10-60% B (buffer A: 0.1% TFA/H_2O, buffer B: 0.1% TFA/CH_3CN) in 60 min., flow rate 8ml/min, detection 280 nm. The main peak was cut by analytical HPLC analysis of collected fractions, pooled and lyophilized to yield 40 mg (25 %) of a white powder. This compound was homogeneous by HPLC. LR-Electrospray $C_{44}H_{57}N_9O_5$ cal: 792 observed: m/z (793 M+H)

EXAMPLE 35

Penta-Apc-(D)Phe-Arg-(2)Nal-Gly-NH_2



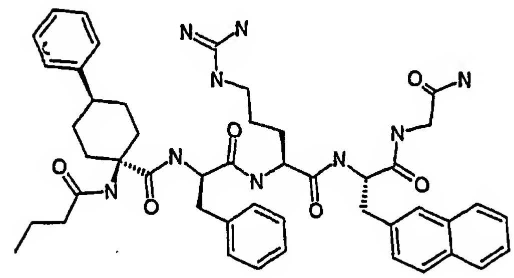
Fmoc-Linker-BHA resin (360 mg, 0.2 mmol) from Example 29 were subjected to solid phase synthesis using protocol 1 described above. All couplings were performed using HBTU in DMF as the coupling agent and DIPEA (3 equiv.) as base. Five coupling cycles were performed of one cycle each with Fmoc-Gly (180 mg, 0.6 mmol) and HBTU (226 mg, 0.6 mmol), Fmoc-2-Nal (260 mg, 0.6 mmol) and HBTU (226 mg, 0.6 mmol), Fmoc-Arg (Pmc) (400 mg, 0.6 mmol) and HBTU (226 mg, 0.6 mmol), Fmoc-(D)Phe (240 mg, 0.6 mmol) and HBTU (226 mg, 0.6 mmol), **Fmoc-Apc** (275 mg 0.6 mmol) and HBTU (226 mg, 0.6 mmol). The peptide resin was carried through steps 1 - 5 of protocol 1, washed with CH_2Cl_2 (three times) and treated with 1 mL valeric anhydride in 6% DIPEA/CH_2Cl_2 30 minutes. The resin was filtered and washed successively with 20 ml each of CH_2Cl_2 (two times), isopropanol, and CH_2Cl_2 (three times). The resin was dried under vacuum to yield 580 mg of Pentyl-Pentapeptide resin.

The Pentyl-Pentapeptide resin was treated with 40 μL ethanedithiol, 40 μL dimethylsulfide, 120 μL anisole, and 4 mL trifluoroacetic acid at room temperature for 180 min. The resin was filtered off, washed with ~2 ml TFA and the filtrates precipitated in chilled ethyl ether. The precipitates were centrifuged and the ether layer decanted. The residue was washed with two or three volumes of Et_2O and recentrifuged and the crude product was dried under vacuum to yield 145 mg of an off-white solid.

This crude material was purified by preparative HPLC on a Vydac C18-column (2.5 x 20 cm) and eluted with a linear gradient of 10-60% B (buffer A: 0.1% TFA/H_2O, buffer B: 0.1% TFA/CH_3CN) in 60 min., flow rate 8ml/min, detection 280 nm. The main peak was cut by analytical HPLC analysis of collected fractions, pooled and lyophilized to yield 61 mg (36 %) of a white, amorphous powder. This compound was homogeneous by HPLC. LR-Electrospray: $C_{48}H_{61}N_9O_6$, cal: 860 observed: m/z (861 M+H).

EXAMPLE 36

Bu-Apc-(D)Phe-Arg-(2)Nal-Gly-NH_2



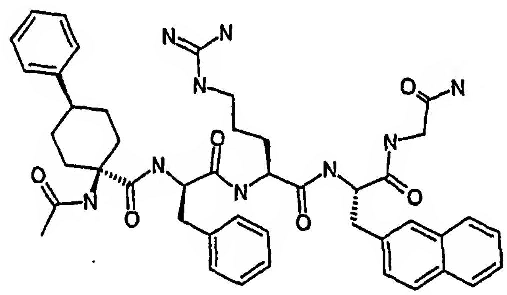
Fmoc-Linker-BHA resin (360 mg, 0.2 mmol) from Example 29 were subjected to solid phase synthesis using protocol 1 described above. All couplings were performed using HBTU in DMF as the coupling agent and DIPEA (3 equiv.) as base. Five coupling cycles were performed of one cycle each with Fmoc-Gly (180 mg, 0.6 mmol) and HBTU (226 mg, 0.6 mmol), **Fmoc-(2)Nal** (265 mg, 0.6 mmol) and HBTU (226 mg, 0.6 mmol), Fmoc-Arg (Pmc) (400 mg, 0.6 mmol) and HBTU (226 mg, 0.6 mmol), Fmoc-(D)Phe (240 mg, 0.6 mmol) and HBTU (226 mg, 0.6 mmol), **Fmoc-Apc** (275 mg 0.6 mmol) and HBTU (226 mg, 0.6 mmol). The peptide resin was carried through steps 1 - 5 of protocol 1, washed with CH_2Cl_2 (three times) and treated with 1 mL acetic anhydride in 6% DIPEA/CH_2Cl_2 30 minutes. The resin was filtered and washed successively with 20 ml each of CH_2Cl_2 (two times), isopropanol, and CH_2Cl_2 (three times). The resin was dried under vacuum to yield 600 mg of Butyl Pentapeptide resin

The butyl-Pentapeptide resin was treated with 40 µL ethanedithiol, 40 µL dimethylsulfide, 120 µL anisole, and 4 mL trifluoroacetic acid at room temperature for 180 min. The resin was filtered off, washed with ~2 ml TFA and the filtrates precipitated in chilled ethyl ether. The precipitates were centrifuged and the ether layer decanted. The residue was washed with two or three volumes of Et_2O and recentrifuged and the crude product was dried under vacuum to yield 144 mg of an off-white solid.

This crude material was purified by preparative HPLC on a Vydac C18-column (2.5 x 20 cm) and eluted with a linear gradient of 10-60% B (buffer A: 0.1% TFA/H_2O, buffer B: 0.1% TFA/CH_3CN) in 60 min., flow rate 8ml/min, detection 280 nm. The main peak was cut by analytical HPLC analysis of collected fractions, pooled and lyophilized to yield 55 mg (32 %) of a white, amorphous powder. This compound was homogeneous by HPLC. LR-Electrospray: $C_{47}H_{59}N_9O_6$, cal 846 observed: m/z (847 M+H).

EXAMPLE 37

Ac-Apc-(D)Phe-Arg-(2)Nal-Gly-NH_2



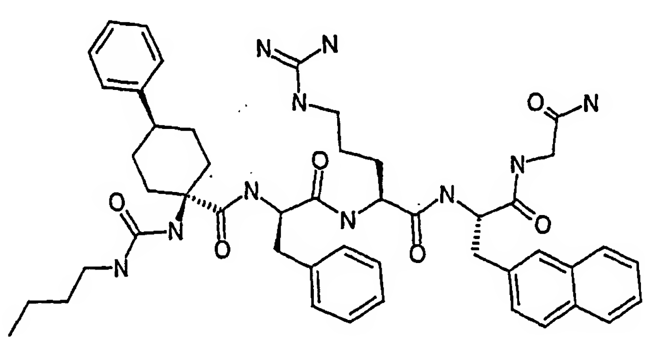
Fmoc-Linker-BHA resin (360 mg, 0.2 mmol) from Example 29 were subjected to solid phase synthesis using protocol 1 described above. All couplings were performed using HBTU in DMF as the coupling agent and DIPEA (3 equiv.) as base. Five coupling cycles were performed of one cycle each with Fmoc-Gly (180 mg, 0.6 mmol) and HBTU (226 mg, 0.6 mmol), **Fmoc-(2)Nal** (265 mg, 0.6 mmol) and HBTU (226 mg, 0.6 mmol), Fmoc-Arg (Pmc) (400 mg, 0.6 mmol) and HBTU (226 mg, 0.6 mmol), Fmoc-(D)Phe (240 mg, 0.6 mmol) and HBTU (226 mg, 0.6 mmol), **Fmoc-Apc** (275 mg 0.6 mmol) and HBTU (226 mg, 0.6 mmol). The peptide resin was carried through steps 1 - 5 of protocol 1, washed with CH_2Cl_2 (three times) and treated with 1 mL acetic anhydride in 6% DIPEA/CH_2Cl_2 30 minutes. The resin was filtered and washed successively with 20 ml each of CH_2Cl_2 (two times), isopropanol, and CH_2Cl_2 (three times). The resin was dried under vacuum to yield 620 mg of Ac-Pentapeptide resin.

The Ac-Pentapeptide resin was treated with 40 µL ethanedithiol, 40 µL dimethylsulfide, 120 µL anisole, and 4 mL trifluoroacetic acid at room temperature for 180 min. The resin was filtered off, washed with ~2 ml TFA and the filtrates precipitated in chilled ethyl ether. The precipitates were centrifuged and the ether layer decanted. The residue was washed with two or three volumes of Et_2O and recentrifuged and the crude product was dried under vacuum to yield 150 mg of an off-white solid.

This crude material was purified by preparative HPLC on a Vydac C18-column (2.5 x 20 cm) and eluted with a linear gradient of 10-60% B (buffer A: 0.1% TFA/H_2O, buffer B: 0.1% TFA/CH_3CN) in 60 min., flow rate 8ml/min, detection 280 nm. The main peak was cut by analytical HPLC analysis of collected fractions, pooled and lyophilized to yield 62 mg (38 %) of a white, amorphous powder. This compound was homogeneous by HPLC. LR-Electrospray: $C_{45}H_{55}N_9O_6$, cal: 818 observed: m/z (819 M+H).

EXAMPLE 38

Bu-Carbamoyl-Apc-(D)Phe-Arg-(2)Nal-Gly-NH_2



Fmoc-Linker-BHA resin (360 mg, 0.2 mmol) from Example 29 were subjected to solid phase synthesis using protocol 1 described above. All couplings were performed using HBTU in DMF as the coupling agent and DIPEA (3 equiv.) as base. Five coupling cycles were performed of one cycle each with Fmo-Gly (180 mg, 0.6 mal) and HBTU (226 mg, 0.6 mal), Fmoc-(2)Nal (265 mg, 0.6 mmol) and HBTU (226 mg, 0.6 mmol), Fmoc-Arg (Pmc) (400 mg, 0.6 mmol) and HBTU (226 mg, 0.6 mmol), Fmoc-(D)Phe (240 mg, 0.6 mmol) and

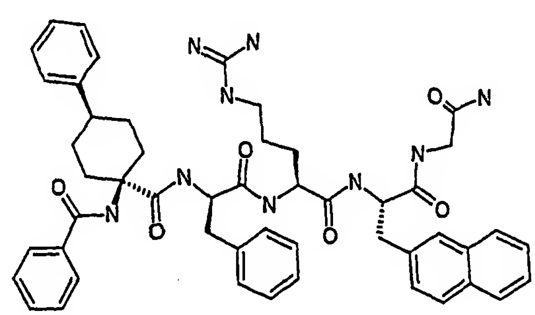
HBTU (226 mg, 0.6 mmol), Fmoc-Apc (275 mg 0.6 mmol) and HBTU (226 mg, 0.6 mmol). The peptide resin was carried through steps 1 - 5 of protocol 1, washed with CH_2Cl_2 (three times) and treated n-butyl isocyante (5eq) in 6% DIPEA/DMF for 12 hours. The resin was filtered and washed successively with 20 ml each of CH_2Cl_2 (two times), isopropanol, and CH_2Cl_2 (three times). The resin was dried under vacuum to yield 550 mg of Butyl carbamoyl-Pentapeptide resin.

The Butyl carbamoyl-Pentapeptide resin was treated with 40 µL ethanedithiol, 40 µL dimethylsulfide, 120 µL anisole, and 4 mL trifluoroacetic acid at room temperature for 180 min. The resin was filtered off, washed with ~2 ml TFA and the filtrates precipitated in chilled ethyl ether. The precipitates were centrifuged and the ether layer decanted. The residue was washed with two or three volumes of Et_2O and recentrifuged and the crude product was dried under vacuum to yield 135 mg of an off-white solid.

This crude material was purified by preparative HPLC on a Vydac C18-column (2.5 x 20 cm) and eluted with a linear gradient of 10-60% B (buffer A: 0.1% TFA/H_2O, buffer B: 0.1% TFA/CH_3CN) in 60 min., flow rate 8ml/min, detection 280 nm. The main peak was cut by analytical HPLC analysis of collected fractions, pooled and lyophilized to yield 55 mg (31 %) of a white, amorphous powder. This compound was homogeneous by HPLC. LR-Electrospray: $C_{48}H_{62}N_{10}O_6$, cal: 875 observed: m/z (876 M+H).

EXAMPLE 39

Benzoyl-Apc-(D)Phe-Arg-(2)Nal-Gly-NH_2



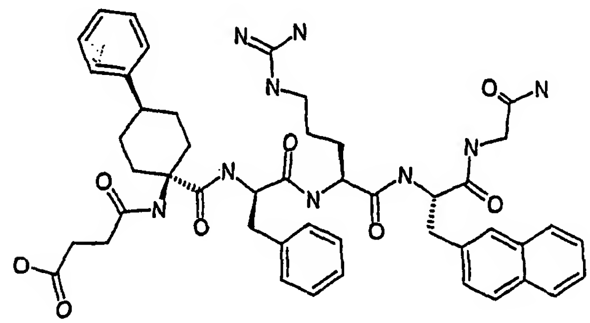
Fmoc-Linker-BHA resin (360 mg, 0.2 mmol) from Example 29 were subjected to solid phase synthesis using protocol 1 described above. All couplings were performed using HBTU in DMF as the coupling agent and DIPEA (3 equiv.) as base. Five coupling cycles were performed of one cycle each with Fmo-Gly (180 mg, 0.6 mal) and HBTU (226 mg, 0.6 mal), **Fmoc-(2)Nal** (265 mg, 0.6 mmol) and HBTU (226 mg, 0.6 mmol), Fmoc-Arg (Pmc) (400 mg, 0.6 mmol) and HBTU (226 mg, 0.6 mmol), Fmoc-(D)Phe (240 mg, 0.6 mmol) and HBTU (226 mg, 0.6 mmol), **Fmoc-Apc** (275 mg 0.6 mmol) and HBTU (226 mg, 0.6 mmol). The peptide resin was carried through steps 1 - 5 of protocol 1, washed with CH_2Cl_2 (three times) and treated benzoic anhydride in 6% DIPEA/DMF for 12 hours. The resin was filtered and washed successively with 20 ml each of CH_2Cl_2 (two times), isopropanol, and CH_2Cl_2 (three times). The resin was dried under vacuum to yield 570 mg of benzoyl-Pentapeptide resin.

The benzoyl-Pentapeptide resin was treated with 40 µL ethanedithiol, 40 µL dimethylsulfide, 120 µL anisole, and 4 mL trifluoroacetic acid at room temperature for 180 min. The resin was filtered off, washed with ~2 ml TFA and the filtrates precipitated in chilled ethyl ether. The precipitates were centrifuged and the ether layer decanted. The residue was washed with two or three volumes of Et_2O and recentrifuged and the crude product was dried under vacuum to yield 130 mg of an off-white solid.

This crude material was purified by preparative HPLC on a Vydac C18-column (2.5 x 20 cm) and eluted with a linear gradient of 10-60% B (buffer A: 0.1% TFA/H_2O, buffer B: 0.1% TFA/CH_3CN) in 60 min., flow rate 8ml/min, detection 280 nm. The main peak was cut by analytical HPLC analysis of collected fractions, pooled and lyophilized to yield 50 mg (28 %) of a white, amorphous powder. This compound was homogeneous by HPLC. LR-Electrospray: $C_{50}H_{57}N_9O_6$, cal: 880 observed: m/z (881 M+H).

EXAMPLE 40

3-carboxylpropanoyl-Apc-(D)Phe-Arg-(2)Nal-Gly-NH_2



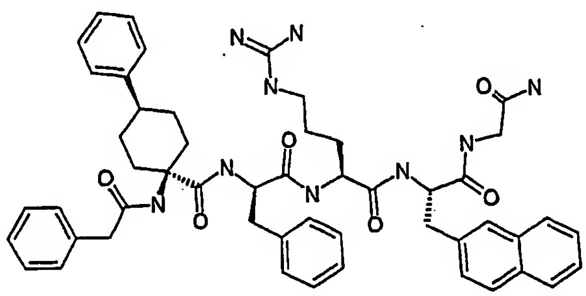
Fmoc-Linker-BHA resin (360 mg, 0.2 mmol) from Example 29 were subjected to solid phase synthesis using protocol 1 described above. All couplings were performed using HBTU in DMF as the coupling agent and DIPEA (3 equiv.) as base. Five coupling cycles were performed of one cycle each with Fmoc-Gly (180 mg, 0.6 mmol) and HBTU (226 mg, 0.6 mmol), **Fmoc-(2)Nal** (265 mg, 0.6 mmol) and HBTU (226 mg, 0.6 mmol), Fmoc-Arg (Pmc) (400 mg, 0.6 mmol) and HBTU (226 mg, 0.6 mmol), Fmoc-(D)Phe (240 mg, 0.6 mmol) and HBTU (226 mg, 0.6 mmol), **Fmoc-Apc** (275 mg 0.6 mmol) and HBTU (226 mg, 0.6 mmol). The peptide resin was carried through steps 1 - 5 of protocol 1, washed with CH_2Cl_2 (three times) and treated with succinic acid (71 mg, 0.6 mmol) and HBTU (226 mg, 0.6 mmol) in DMF. The resin was filtered and washed successively with 20 ml each of CH_2Cl_2 (two times), isopropanol, and CH_2Cl_2 (three times). The resin was dried under vacuum to yield 550 mg of 3-carboxypropanoyl-Pentapeptide resin.

The 3-carboxypropanoyl-Pentapeptide resin was treated with 40 μL ethanedithiol, 40 μL dimethylsulfide, 120 μL anisole, and 4 mL trifluoroacetic acid at room temperature for 180 min. The resin was filtered off, washed with ~2 ml TFA and the filtrates precipitated in chilled ethyl ether. The precipitates were centrifuged and the ether layer decanted. The residue was washed with two or three volumes of Et_2O and recentrifuged and the crude product was dried under vacuum to yield 136 mg of an off-white solid.

This crude material was purified by preparative HPLC on a Vydac C18-column (2.5 x 20 cm) and eluted with a linear gradient of 10-60% B (buffer A: 0.1% TFA/H_2O, buffer B: 0.1% TFA/CH_3CN) in 60 min., flow rate 8ml/min, detection 280 nm. The main peak was cut by analytical HPLC analysis of collected fractions, pooled and lyophilized to yield 52 mg (30 %) of a white, amorphous powder. This compound was homogeneous by HPLC. LR-Electrospray: $C_{47}H_{57}N_9O_8$, cal: 876 observed: m/z (877 M+H).

EXAMPLE 41

Phenylacetyl-Apc-(D)Phe-Arg-(2)Nal-Gly-NH$_2$



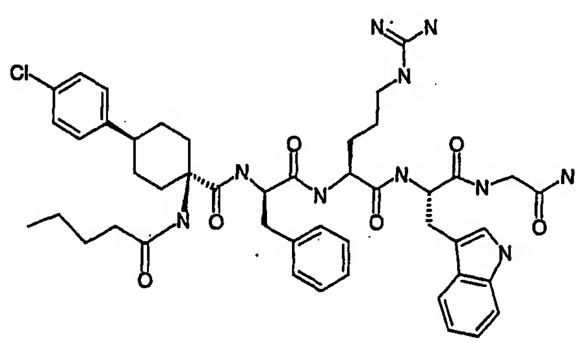
Fmoc-Linker-BHA resin (360 mg, 0.2 mmol) from Example 29 were subjected to solid phase synthesis using protocol 1 described above. All couplings were performed using HBTU in DMF as the coupling agent and DIPEA (3 equiv.) as base. Five coupling cycles were performed of one cycle each with Fmoc-Gly (180 mg, 0.6 mmol) and HBTU (226 mg, 0.6 mmol), **Fmoc-(2)Nal** (265 mg, 0.6 mmol) and HBTU (226 mg, 0.6 mmol), Fmoc-Arg (Pmc) (400 mg, 0.6 mmol) and HBTU (226 mg, 0.6 mmol), Fmoc-(D)Phe (240 mg, 0.6 mmol) and HBTU (226 mg, 0.6 mmol), **Fmoc-Apc** (275 mg 0.6 mmol) and HBTU (226 mg, 0.6 mmol). The peptide resin was carried through steps 1 - 5 of protocol 1, washed with CH_2Cl_2 (three times) and treated with phenylacetic acid (82 mg, 0.6 mmol) and HBTU (226 mg, 0.6 mmol) in DMF. The resin was filtered and washed successively with 20 ml each of CH_2Cl_2 (two times), isopropanol, and CH_2Cl_2 (three times). The resin was dried under vacuum to yield 580 mg of Phenylacetyl-Pentapeptide resin.

The phenylacetyl-Pentapeptide resin was treated with 40 μL ethanedithiol, 40 μL dimethylsulfide, 120 μL anisole, and 4 mL trifluoroacetic acid at room temperature for 180 min. The resin was filtered off, washed with ~2 ml TFA and the filtrates precipitated in chilled ethyl ether. The precipitates were centrifuged and the ether layer decanted. The residue was washed with two or three volumes of Et_2O and recentrifuged and the crude product was dried under vacuum to yield 132 mg of an off-white solid.

This crude material was purified by preparative HPLC on a Vydac C18-column (2.5 x 20 cm) and eluted with a linear gradient of 10-60% B (buffer A: 0.1% TFA/H_2O, buffer B: 0.1% TFA/CH_3CN) in 60 min., flow rate 8ml/min, detection 280 nm. The main peak was cut by analytical HPLC analysis of collected fractions, pooled and lyophilized to yield 49 mg (29 %) of a white, amorphous powder. This compound was homogeneous by HPLC. LR-Electrospray: $C_{51}H_{59}N_9O_6$, cal: 894 observed: m/z (895 M+H).

EXAMPLE 42

Penta-**4-ClApc**-(D)Phe-Arg-Trp-Gly-NH_2



Fmoc-Linker-BHA resin (360 mg, 0.2 mmol) from Example 29 were subjected to solid phase synthesis using protocol 1 described above. All couplings were performed using HBTU in DMF as the coupling agent and DIPEA (3 equiv.) as base. Five coupling cycles were performed of one cycle each with Fmoc-Gly (180 mg, 0.6 mmol) and HBTU (226 mg, 0.6 mmol), Fmoc-Trp (260 mg, 0.6 mmol) and HBTU (226 mg, 0.6 mmol), Fmoc-Arg (Pmc) (400 mg, 0.6 mmol) and HBTU (226 mg, 0.6 mmol), Fmoc-(D)Phe (240 mg, 0.6 mmol) and

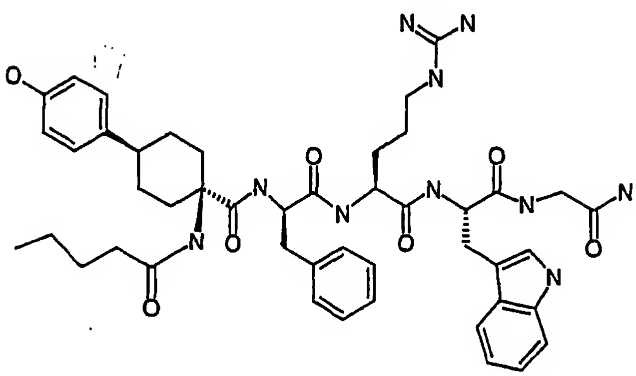
HBTU (226 mg, 0.6 mmol), **Fmoc-4-ClApc** (275 mg 0.6 mmol) and HBTU (226 mg, 0.6 mmol). The peptide resin was carried through steps 1 - 5 of protocol 1, washed with CH_2Cl_2 (three times) and treated with 1 mL valeric anhydride in 6% DIPEA/CH_2Cl_2 for 30 minutes. The resin was filtered and washed successively with 20 ml each of CH_2Cl_2 (two times), isopropanol, and CH_2Cl_2 (three times). The resin was dried under vacuum to yield 620 mg of Pentyl-Pentapeptide resin.

The Pentyl-Pentapeptide resin was treated with 40 µL ethanedithiol, 40 µL dimethylsulfide, 120 µL anisole, and 4 mL trifluoroacetic acid at room temperature for 180 min. The resin was filtered off, washed with ~2 ml TFA and the filtrates precipitated in chilled ethyl ether. The precipitates were centrifuged and the ether layer decanted. The residue was washed with two or three volumes of Et_2O and recentrifuged and the crude product was dried under vacuum to yield 141 mg of an off-white solid.

This crude material was purified by preparative HPLC on a Vydac C18-column (2.5 x 20 cm) and eluted with a linear gradient of 10-60% B (buffer A: 0.1% TFA/H_2O, buffer B: 0.1% TFA/CH_3CN) in 60 min., flow rate 8ml/min, detection 280 nm. The main peak was cut by analytical HPLC analysis of collected fractions, pooled and lyophilized to yield 45 mg (26 %) of a white, amorphous powder. This compound was homogeneous by HPLC. LR-Electrospray: $C_{46}H_{59}N_{10}O_6Cl$, cal: 883 observed: m/z (884 M+H).

EXAMPLE 43

Penta-4-HOApc-(D)Phe-Arg-Trp-Gly-NH_2



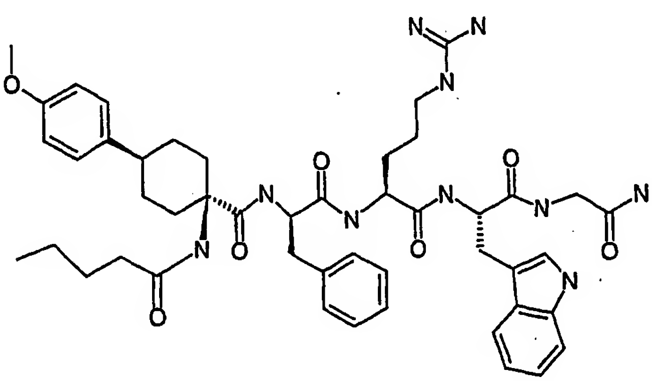
Fmoc-Linker-BHA resin (360 mg, 0.2 mmol) from Example 29 were subjected to solid phase synthesis using protocol 1 described above. All couplings were performed using HBTU in DMF as the coupling agent and DIPEA (3 equiv.) as base. Five coupling cycles were performed of one cycle each with Fmoc-Gly (180 mg, 0.6 mmol) and HBTU (226 mg, 0.6 mmol), Fmoc-Trp (260 mg, 0.6 mmol) and HBTU (226 mg, 0.6 mmol), Fmoc-Arg (Pmc) (400 mg, 0.6 mmol) and HBTU (226 mg, 0.6 mmol), Fmoc-(D)Phe (240 mg, 0.6 mmol) and HBTU (226 mg, 0.6 mmol), **Fmoc-4-HOApc** (280 mg 0.6 mmol) and HBTU (226 mg, 0.6 mmol). The peptide resin was carried through steps 1 - 5 of protocol 1, washed with CH_2Cl_2 (three times) and treated with 1 mL valeric anhydride in 6% DIPEA/CH_2Cl_2 for 30 minutes. The resin was filtered and washed successively with 20 ml each of CH_2Cl_2 (two times), isopropanol, and CH_2Cl_2 (three times). The resin was dried under vacuum to yield 620 mg of Pentyl-Pentapeptide resin.

The Pentyl-Pentapeptide resin was treated with 40 µL ethanedithiol, 40 µL dimethylsulfide, 120 µL anisole, and 4 mL trifluoroacetic acid at room temperature for 180 min. The resin was filtered off, washed with ~2 ml TFA and the filtrates precipitated in chilled ethyl ether. The precipitates were centrifuged and the ether layer decanted. The residue was washed with two or three volumes of Et_2O and recentrifuged and the crude product was dried under vacuum to yield 150 mg of an off-white solid.

This crude material was purified by preparative HPLC on a Vydac C18-column (2.5 x 20 cm) and eluted with a linear gradient of 10-60% B (buffer A: 0.1% TFA/H_2O, buffer B: 0.1% TFA/CH_3CN) in 60 min., flow rate 8ml/min, detection 280 nm. The main peak was cut by analytical HPLC analysis of collected fractions, pooled and lyophilized to yield 55 mg (31 %) of a white, amorphous powder. This compound was homogeneous by HPLC. LR-Electrospray: $C_{46}H_{60}N_{10}O_7$, cal: 865 observed: m/z (866 M+H).

EXAMPLE 44

Penta-4-MeOApc-(D)Phe-Arg-Trp-Gly-NH_2



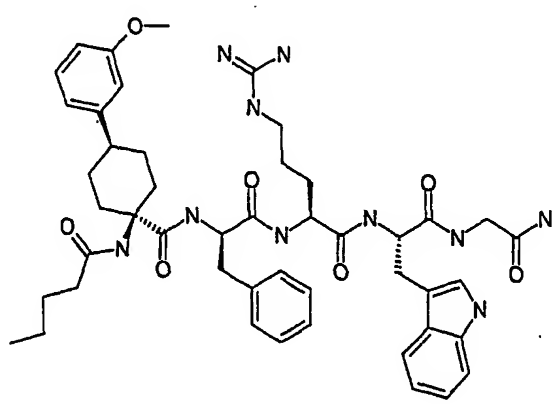
Fmoc-Linker-BHA resin (360 mg; 0.2 mmol) from Example 29 were subjected to solid phase synthesis using protocol 1 described above. All couplings were performed using HBTU in DMF as the coupling agent and DIPEA (3 equiv.) as base. Five coupling cycles were performed of one cycle each with Fmoc-Gly (180 mg, 0.6 mmol) and HBTU (226 mg, 0.6 mmol), Fmoc-Trp (260 mg, 0.6 mmol) and HBTU (226 mg, 0.6 mmol), Fmoc-Arg (Pmc) (400 mg, 0.6 mmol) and HBTU (226 mg, 0.6 mmol), Fmoc-(D)Phe (240 mg, 0.6 mmol) and HBTU (226 mg, 0.6 mmol), **Fmoc-4-MeOApc** (300 mg 0.6 mmol) and HBTU (226 mg, 0.6 mmol),. The peptide resin was carried through steps 1 - 5 of protocol 1, washed with CH_2Cl_2 (three times) and treated with 1 mL valeric anhydride in 6% DIPEA/CH_2Cl_2 for 30 minutes. The resin was filtered and washed successively with 20 ml each of CH_2Cl_2 (two times), isopropanol, and CH_2Cl_2 (three times). The resin was dried under vacuum to yield 610 mg of Pentyl-Pentapeptide resin.

The Pentyl-Pentapeptide resin was treated with 40 µL ethanedithiol, 40 µL dimethylsulfide, 120 µL anisole, and 4 mL trifluoroacetic acid at room temperature for 180 min. The resin was filtered off, washed with ~2 ml TFA and the filtrates precipitated in chilled ethyl ether. The precipitates were centrifuged and the ether layer decanted. The residue was washed with two or three volumes of Et_2O and recentrifuged and the crude product was dried under vacuum to yield 152 mg of an off-white solid.

This crude material was purified by preparative HPLC on a Vydac C18-column (2.5 x 20 cm) and eluted with a linear gradient of 10-60% B (buffer A: 0.1% TFA/H_2O, buffer B: 0.1% TFA/CH_3CN) in 60 min., flow rate 8ml/min, detection 280 nm. The main peak was cut by analytical HPLC analysis of collected fractions, pooled and lyophilized to yield 59 mg (33 %) of a white, amorphous powder. This compound was homogeneous by HPLC. LR-Electrospray: $C_{47}H_{62}N_{10}O_7$, cal: 879 observed: 880 m/z (M+H).

EXAMPLE 45

Penta-3-MeOApc-(D)Phe-Arg-Trp-Gly-NH_2



Fmoc-Linker-BHA resin (360 mg, 0.2 mmol) from Example 29 were subjected to solid phase synthesis using protocol 1 described above. All couplings were performed using HBTU in DMF as the coupling agent and DIPEA (3 equiv.) as base. Five coupling cycles were

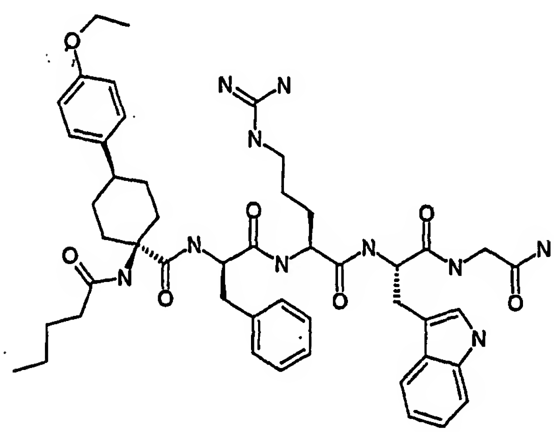
performed of one cycle each with Fmoc-Gly (180 mg, 0.6 mmol) and HBTU (226 mg, 0.6 mmol), Fmoc-Trp (260 mg, 0.6 mmol) and HBTU (226 mg, 0.6 mmol), Fmoc-Arg (Pmc) (400 mg, 0.6 mmol) and HBTU (226 mg, 0.6 mmol), Fmoc-(D)Phe (240 mg, 0.6 mmol) and HBTU (226 mg, 0.6 mmol), **Fmoc-3-MeOApc** (300 mg 0.6 mmol) and HBTU (226 mg, 0.6 mmol),. The peptide resin was carried through steps 1 - 5 of protocol 1, washed with CH_2Cl_2 (three times) and treated with 1 mL valeric anhydride in 6% DIPEA/CH_2Cl_2 for 30 minutes. The resin was filtered and washed successively with 20 ml each of CH_2Cl_2 (two times), isopropanol, and CH_2Cl_2 (three times). The resin was dried under vacuum to yield 610 mg of Pentyl-Pentapeptide resin.

The Pentyl-Pentapeptide resin was treated with 40 μL ethanedithiol, 40 μL dimethylsulfide, 120 μL anisole, and 4 mL trifluoroacetic acid at room temperature for 180 min. The resin was filtered off, washed with ~2 ml TFA and the filtrates precipitated in chilled ethyl ether. The precipitates were centrifuged and the ether layer decanted. The residue was washed with two or three volumes of Et_2O and recentrifuged and the crude product was dried under vacuum to yield 152 mg of an off-white solid.

This crude material was purified by preparative HPLC on a Vydac C18-column (2.5 x 20 cm) and eluted with a linear gradient of 10-60% B (buffer A: 0.1% TFA/H_2O, buffer B: 0.1% TFA/CH_3CN) in 60 min., flow rate 8ml/min, detection 280 nm. The main peak was cut by analytical HPLC analysis of collected fractions, pooled and lyophilized to yield 59 mg (33 %) of a white, amorphous powder. This compound was homogeneous by HPLC. LR-Electrospray: $C_{47}H_{62}N_{10}O_7$, cal: 879 observed: 880 m/z (M+H).

EXAMPLE 46

Penta-4-EtOApc-(D)Phe-Arg-Trp-Gly-NH_2



Fmoc-Linker-BHA resin (360 mg, 0.2 mmol) from Example 29 were subjected to solid phase synthesis using protocol 1 described above. All couplings were performed using HBTU in DMF as the coupling agent and DIPEA (3 equiv.) as base. Five coupling cycles were performed of one cycle each with Fmoc-Gly (180 mg, 0.6 mmol) and HBTU (226 mg, 0.6 mmol), Fmoc-Trp (260 mg, 0.6 mmol) and HBTU (226 mg, 0.6 mmol), Fmoc-Arg (Pmc) (400 mg, 0.6 mmol) and HBTU (226 mg, 0.6 mmol), Fmoc-(D)Phe (240 mg, 0.6 mmol) and HBTU (226 mg, 0.6 mmol), **Fmoc-4-EtOApc** (320 mg 0.6 mmol) and HBTU (226 mg, 0.6 mmol). The peptide resin was carried through steps 1 - 5 of protocol 1, washed with CH_2Cl_2 (three times).and treated with 1 mL valeric anhydride in 6% DIPEA/CH_2Cl_2 for 30 minutes. The resin was filtered and washed successively with 20 ml each of CH_2Cl_2 (two times), isopropanol, and CH_2Cl_2 (three times). The resin was dried under vacuum to yield 615 mg of Pentyl-Pentapeptide resin.

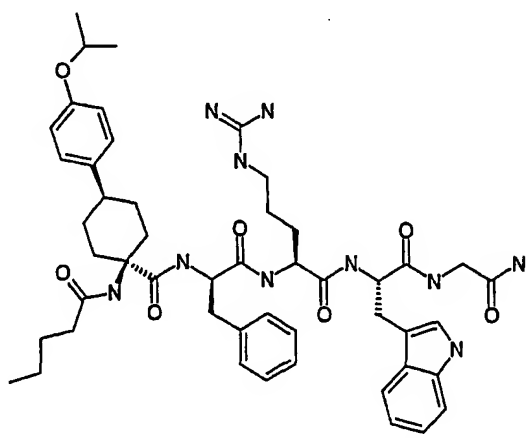
The Pentyl-Pentapeptide resin was treated with 40 µL ethanedithiol, 40 µL dimethylsulfide, 120 µL anisole, and 4 mL trifluoroacetic acid at room temperature for 180 min. The resin was filtered off, washed with ~2 ml TFA and the filtrates precipitated in chilled ethyl ether. The precipitates were centrifuged and the ether layer decanted. The

residue was washed with two or three volumes of Et_2O and recentrifuged and the crude product was dried under vacuum to yield 160 mg of an off-white solid.

This crude material was purified by preparative HPLC on a Vydac C18-column (2.5 x 20 cm) and eluted with a linear gradient of 10-60% B (buffer A: 0.1% TFA/H_2O, buffer B: 0.1% TFA/CH_3CN) in 60 min., flow rate 8ml/min, detection 280 nm. The main peak was cut by analytical HPLC analysis of collected fractions, pooled and lyophilized to yield 63 mg (35 %) of a white, amorphous powder. This compound was homogeneous by HPLC. LR-Electrospray: $C_{48}H_{64}N_{10}O_7$, cal: 893 observed: 894 m/z (M+H).

EXAMPLE 47

Penta-**4-iPrOApc**-(D)Phe-Arg-Trp-Gly-NH_2



Fmoc-Linker-BHA resin (360 mg, 0.2 mmol) from Example 29 were subjected to solid phase synthesis using protocol 1 described above. All couplings were performed using HBTU in DMF as the coupling agent and DIPEA (3 equiv.) as base. Five coupling cycles were performed of one cycle each with Fmoc-Gly (180 mg, 0.6 mmol) and HBTU (226 mg, 0.6 mmol), Fmoc-Trp (260 mg, 0.6 mmol) and HBTU (226 mg, 0.6 mmol), Fmoc-Arg (Pmc) (400 mg, 0.6 mmol) and HBTU (226 mg, 0.6 mmol), Fmoc-(D)Phe (240 mg, 0.6 mmol) and HBTU (226 mg, 0.6 mmol), **Fmoc-4-iPrOApc** (285 mg 0.6 mmol) and HBTU (226 mg, 0.6 mmol). The peptide resin was carried through steps 1 - 5 of protocol 1, washed with CH_2Cl_2

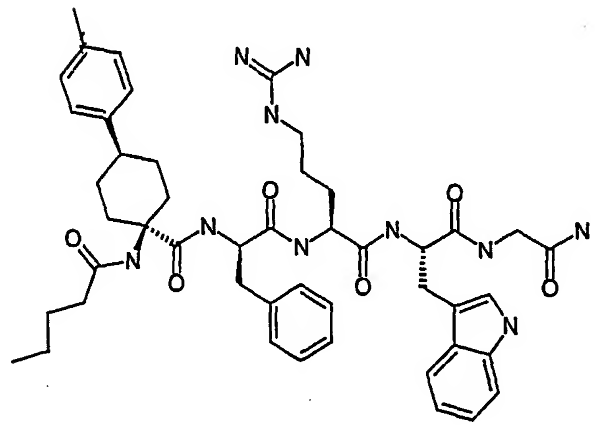
(three times) and treated with 1 mL valeric anhydride in 6% DIPEA/CH_2Cl_2 for 30 minutes. The resin was filtered and washed successively with 20 ml each of CH_2Cl_2 (two times), isopropanol, and CH_2Cl_2 (three times). The resin was dried under vacuum to yield 600 mg of Pentyl-Pentapeptide resin.

The Pentyl-Pentapeptide resin was treated with 40 µL ethanedithiol, 40 µL dimethylsulfide, 120 µL anisole, and 4 mL trifluoroacetic acid at room temperature for 180 min. The resin was filtered off, washed with ~2 ml TFA and the filtrates precipitated in chilled ethyl ether. The precipitates were centrifuged and the ether layer decanted. The residue was washed with two or three volumes of Et_2O and recentrifuged and the crude product was dried under vacuum to yield 140 mg of an off-white solid.

This crude material was purified by preparative HPLC on a Vydac C18-column (2.5 x 20 cm) and eluted with a linear gradient of 10-60% B (buffer A: 0.1% TFA/H_2O, buffer B: 0.1% TFA/CH_3CN) in 60 min., flow rate 8ml/min, detection 280 nm. The main peak was cut by analytical HPLC analysis of collected fractions, pooled and lyophilized to yield 45mg (26 %) of a white, amorphous powder. This compound was homogeneous by HPLC. LR-Electrospray: $C_{49}H_{66}N_{10}O_7$, cal: 907 observed: m/z (908 M+H).

EXAMPLE 48

Penta-4-MeApc-(D)Phe-Arg-Trp-Gly-NH_2



Fmoc-Linker-BHA resin (360 mg, 0.2 mmol) from Example 29 were subjected to solid phase synthesis using protocol 1 described above. All couplings were performed using HBTU in DMF as the coupling agent and DIPEA (3 equiv.) as base. Five coupling cycles were performed of one cycle each with Fmoc-Gly (180 mg, 0.6 mmol) and HBTU (226 mg, 0.6 mmol), Fmoc-Trp (260 mg, 0.6 mmol) and HBTU (226 mg, 0.6 mmol), Fmoc-Arg (Pmc) (400 mg, 0.6 mmol) and HBTU (226 mg, 0.6 mmol), Fmoc-(D)Phe (240 mg, 0.6 mmol) and HBTU (226 mg, 0.6 mmol), **Fmoc-4-MeApc** (280 mg 0.6 mmol) and HBTU (226 mg, 0.6 mmol). The peptide resin was carried through steps 1 - 5 of protocol 1, washed with CH_2Cl_2 (three times) and treated with 1 mL valeric anhydride in 6% DIPEA/CH_2Cl_2 for 30 minutes. The resin was filtered and washed successively with 20 ml each of CH_2Cl_2 (two times), isopropanol, and CH_2Cl_2 (three times). The resin was dried under vacuum to yield 590 mg of Pentyl-Pentapeptide resin.

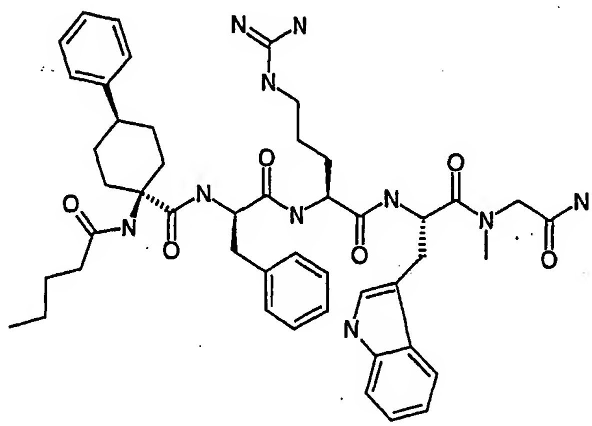
The Pentyl-Pentapeptide resin was treated with 40 µL ethanedithiol, 40 µL dimethylsulfide, 120 µL anisole, and 4 mL trifluoroacetic acid at room temperature for 180 min. The resin was filtered off, washed with ~2 ml TFA and the filtrates precipitated in chilled ethyl ether. The precipitates were centrifuged and the ether layer decanted. The

residue was washed with two or three volumes of Et_2O and recentrifuged and the crude product was dried under vacuum to yield 139 mg of an off-white solid.

This crude material was purified by preparative HPLC on a Vydac C18-column (2.5 x 20 cm) and eluted with a linear gradient of 10-60% B (buffer A: 0.1% TFA/H_2O, buffer B: 0.1% TFA/CH_3CN) in 60 min., flow rate 8ml/min, detection 280 nm. The main peak was cut by analytical HPLC analysis of collected fractions, pooled and lyophilized to yield 51mg (30 %) of a white, amorphous powder. This compound was homogeneous by HPLC. LR-Electrospray: $C_{47}H_{62}N_{10}O_6$, cal: 863 observed: m/z (864 M+H).

EXAMPLE 49

Penta-**Apc**-(D)Phe-Arg-Trp-**Sar**-NH_2



Fmoc-Linker-BHA resin (360 mg, 0.2 mmol) from Example 29 were subjected to solid phase synthesis using protocol 1 described above. All couplings were performed using HBTU in DMF as the coupling agent and DIPEA (3 equiv.) as base. Five coupling cycles were performed of one cycle each with **Fmoc-Sar** (187mg, 0.6 mmol) and HBTU (226 mg, 0.6 mmol), Fmoc-Trp (260 mg, 0.6 mmol) and HBTU (226 mg, 0.6 mmol), Fmoc-Arg (Pmc) (400 mg, 0.6 mmol) and HBTU (226 mg, 0.6 mmol), Fmoc-(D)Phe (240 mg, 0.6 mmol) and HBTU (226 mg, 0.6 mmol), Fmoc-Apc (275 mg 0.6 mmol) and HBTU (226 mg, 0.6 mmol). The peptide resin was carried through steps 1 - 5 of protocol 1, washed with CH_2Cl_2 (three

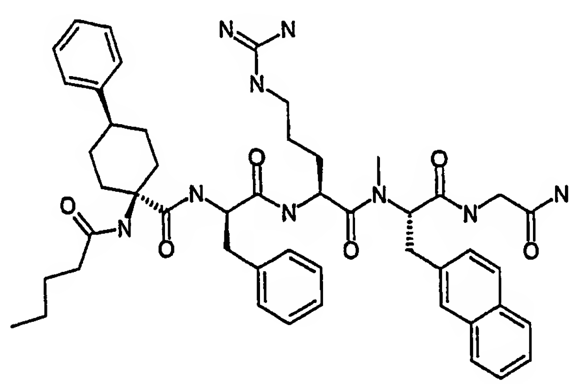
times) and treated with 1 mL valeric anhydride in 6% DIPEA/CH_2Cl_2 for 30 minutes. The resin was filtered and washed successively with 20 ml each of CH_2Cl_2 (two times), isopropanol, and CH_2Cl_2 (three times). The resin was dried under vacuum to yield 620 mg of Pentyl-Pentapeptide resin.

The Pentyl-Pentapeptide resin was treated with 40 µL ethanedithiol, 40 µL dimethylsulfide, 120 µL anisole, and 4 mL trifluoroacetic acid at room temperature for 180 min. The resin was filtered off, washed with ~2 ml TFA and the filtrates precipitated in chilled ethyl ether. The precipitates were centrifuged and the ether layer decanted. The residue was washed with two or three volumes of Et_2O and recentrifuged and the crude product was dried under vacuum to yield 175 mg of an off-white solid.

This crude material was purified by preparative HPLC on a Vydac C18-column (2.5 x 20 cm) and eluted with a linear gradient of 10-60% B (buffer A: 0.1% TFA/H_2O, buffer B: 0.1% TFA/CH_3CN) in 60 min., flow rate 8ml/min, detection 280 nm. The main peak was cut by analytical HPLC analysis of collected fractions, pooled and lyophilized to yield 69 mg (40%) of a white, amorphous powder. This compound was homogeneous by HPLC. LR-Electrospray: $C_{47}H_{62}N_{10}O_6$, cal: 863 observed: 864 m/z (M+H).

EXAMPLE 50

Penta-Apc-(D)Phe-Arg-N-methyl (2)Nal-Gly-NH_2

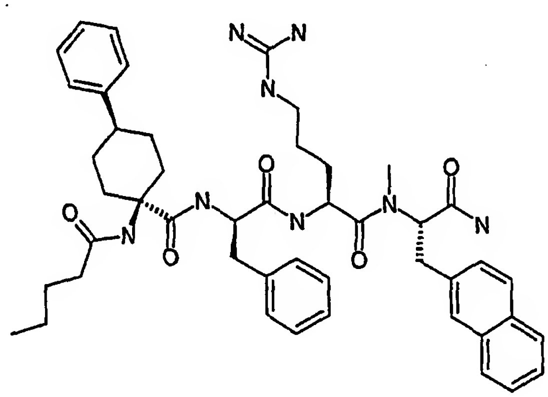


Fmoc-Linker-BHA resin (700 mg, 0.385 mmol) synthesized using the procedure in Example 29 was subjected to solid phase synthesis using DIC / HOBT coupling conditions and washings were performed as shown in protocol 1. All amino acid couplings were performed using DIC (5 eq.), HOBT (2.5 eq.) as the coupling reagents and the Fmoc-amino acid (2.5 eq.). The resin was subjected to washing steps 1-6 as shown in protocol 1, after each peptide coupling. Two coupling cycles were performed, one each with Fmoc-Gly (286 mg, 0.96 mmol) followed by **Fmoc-(2)Nal** (421 mg, 0.96 mmol). After Fmoc removal from 2-Nal residue, the resulting amine was converted to it's 2-nitrobenzene sulfonyl derivative using 2-nitrobenzenesulfonyl chloride (5 eq., 426 mg, 1.93 mmol) and DIPEA (5 eq.) as the base in DMF. Washings were performed using DMF (6 x 30 ml) followed by CH_2Cl_2 (3 x 30 ml) and the resin was dried under vacuum. The sulfonamide obtained was subjected to methylation using triphenylphosphine (5 eq., 505 mg, 1.93 mmol), N, N-diethylazodicarboxylate (5 eq., 303 µl, 1.93 mmol) and methanol (10eq. 156 µl, 3.85 mmol) in THF. Washings were performed using THF (6 x 30 ml) followed by CH_2Cl_2 (5 x 30 ml) and the resin was dried under vacuum. The 2-nitrobenzene sulfonyl group was then removed using 1,8-Diazabicyclo [5.4.0].undec-7-ene (3 eq., 173 µl, 1.16 mmol), 2-mercaptoethanol (5eq. 135 µl, 1.93 mmol) in DMF. Washings were performed using DMF (3 x 30 ml), isopropanol (3-x 30 ml) followed by ethyl ether (3-x 30 ml) and the resin was dried under vacuum. The resulting N-Me-(2)Nal residue was subjected to three coupling cycles, one cycle each with Fmoc-Arg (Pmc) (638 mg, 0.96 mmol), Fmoc-(D)Phe (373 mg, 0.96 mmol) and Fmoc-Apc (170 mg, 0.96 mmol). The peptide resin was carried through steps 1 - 5 of protocol 1, washed with CH_2Cl_2 (three times) and treated with 300 µl valeric anhydride, 245 µl pyridine in 15 ml DMF for 5h. The resin was filtered and washed successively with 30 ml each of DMF (three times), isopropanol, CH_2Cl_2 (three times) and ethyl ether (3 times). The resulting pentyl-peptide resin was dried under vacuum and treated with 7 ml of 60 % trifluoroacetic acid in CH_2Cl_2, 1 % water and 615 ml triethylsilane (10 eq., 3.85 mmol) for 160 minutes. The resin was filtered off, washed with ~5-7 ml CH_2Cl_2, and the filtrates were concentrated on a Savant speed vacuum pump to yield the crude product.

This crude material was purified by preparative HPLC on a Vydac C18-column (2.5 x 20 cm) and eluted with a linear gradient of 10-60% B (buffer A: 0.1% TFA/H_2O, buffer B: 0.1% TFA/CH_3CN) in 60 min., flow rate 8ml/min, detection 280 nm. The main peak was cut by analytical HPLC analysis of collected fractions, pooled and lyophilized to yield 30 mg (~10 %) of a white, amorphous powder. This compound was homogeneous by HPLC. LR-Electrospray: $C_{49}H_{63}N_9O_6$, cal: 873 observed: m/z (874 M+H).

EXAMPLE 51

Penta-Apc-(D)Phe-Arg-N-**methyl** (2) Nal-NH_2



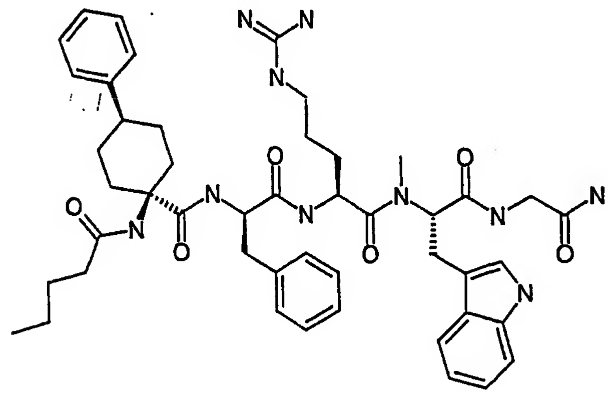
Fmoc-Linker-BHA resin (700 mg, 0.385 mmol) synthesized using the procedure in Example 29 was subjected to solid phase synthesis using DIC / HOBT coupling conditions and washings were performed as shown in protocol 1. All amino acid couplings were performed using DIC (5 eq.), HOBT (2.5 eq.) as the coupling reagents and the Fmoc-amino acid (2.5 eq.) The resin was subjected to washing steps 1-6 as shown in protocol 1, after each peptide coupling. One coupling cycle was performed with **Fmoc-(2)Nal** (421 mg, 0.96 mmol). After Fmoc removal from (2)Nal residue, the resulting amine was converted to it's 2-nitrobenzene sulfonyl derivative using 2-nitrobenzenesulfonyl chloride (5 eq., 426 mg, 1.93 mmol) and DIPEA (5 eq.) as the base in DMF. Washings were performed using DMF (6 x 30 ml) followed by CH_2Cl_2 (3 x 30 ml) and the resin was dried under vacuum. The sulfonamide obtained was subjected to methylation using triphenylphosphine (5 eq., 505 mg, 1.93 mmol), N, N-diethylazodicarboxylate (5 eq., 303 µl, 1.93 mmol) and methanol (10eq.

156 µl, 3.85 mmol) in THF. Washings were performed using THF (6 x 30 ml) followed by CH_2Cl_2 (5 x 30 ml) and the resin was dried under vacuum. The 2-nitrobenzene sulfonyl group was then removed using 1,8-diazabicyclo [5.4.0] undec-7-ene (3 eq., 173 µl, 1.16 mmol), 2-mercaptoethanol, (5eq. 135 µl, 1.93 mmol) in DMF. Washings were performed using DMF (3 x 30 ml), isopropanol (3 x 30 ml) followed by ethyl ether (3 x 30 ml) and the resin was dried under vacuum. The resulting N-Me-(2)Nal residue was subjected to three coupling cycles, one cycle each with Fmoc-Arg (Pmc) (638 mg, 0.96 mmol), Fmoc- (D)Phe (373 mg, 0.96 mmol) and Fmoc-Apc (170 mg 0.96 mmol). The peptide resin was carried through steps 1 - 5 of protocol 1, washed with CH_2Cl_2 (three times) and treated with 300 µl valeric anhydride, 245 µl pyridine in 15 ml DMF for 5h. The resin was filtered and washed successively with 30 ml each of DMF (three times), isopropanol, CH_2Cl_2 (three times) and ethyl ether (3 times). The resulting pentyl-peptide resin was dried under vacuum and treated with 7 ml of 60 % trifluoroacetic acid in CH_2Cl_2, 1 % water and 615 ml triethylsilane (10 eq., 3.85 mmol) for 160 minutes. The resin was filtered off, washed with ~5-7 ml CH_2Cl_2, and the filtrates were concentrated on a Savant speed vacuum pump to yield the crude product.

This crude material was purified by preparative HPLC on a Vydac C18-column (2.5 x 20 cm) and eluted with a linear gradient of 10-60% B (buffer A: 0.1% TFA/H_2O, buffer B: 0.1% TFA/CH_3CN) in 60 min., flow rate 8ml/min, detection 280 nm . The main peak was cut by analytical HPLC analysis of collected fractions, pooled and lyophilized to yield 43 mg (~14 %) of a white, amorphous powder. This compound was homogeneous by HPLC. LR-Electrospray: $C_{47}H_{60}N_8O_5$, cal: 817 observed: m/z (818 M+H).

EXAMPLE 52

Penta-Apc-(D)Phe-Arg-N-methylTrp-Gly-NH_2



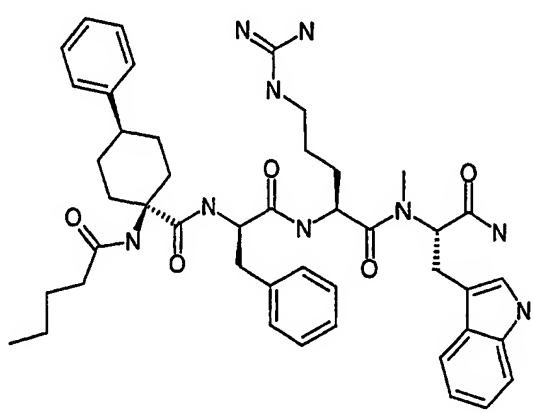
Fmoc-Linker-BHA resin (700 mg, 0.385 mmol) synthesized using the procedure in Example 29 was subjected to solid phase synthesis using DIC / HOBT coupling conditions and washings were performed as shown in the protocol 1. All amino acid couplings were performed using DIC (5 eq.), HOBT (2.5 eq.) as the coupling reagents and the Fmoc-amino acid (2.5 eq.) The resin was subjected to washing steps 1-6 as shown in protocol 1, after each peptide coupling. Two coupling cycles were performed, one each with Fmoc-Gly (286 mg, 0.96 mmol) followed by Fmoc-Trp (461 mg, 0.96 mmol). After Fmoc removal from Trp residue, the resulting amine was converted to its 2-nitrobenzene sulfonyl derivative using 2-nitrobenzenesulfonyl chloride (5 eq., 426 mg, 1.93 mmol) and DIPEA (5 eq.) as the base in DMF. Washings were performed using DMF (6 x 30 ml) followed by CH_2Cl_2 (3 x 30 ml) and the resin was dried under vacuum. The sulfonamide obtained was subjected to methylation using triphenylphosphine (5 eq., 505 mg, 1.93 mmol), N, N-diethylazodicarboxylate (5 eq., 303 µl, 1.93 mmol) and methanol (10eq. 156 µl, 3.85 mmol) in THF. Washings were performed using THF (6 x 30 ml) followed by CH_2Cl_2 (5 x 30 ml) and the resin was dried under vacuum. The 2-nitrobenzene sulfonyl group was then removed using 1,8-diazabicyclo [5.4.0] undec-7-ene (3 eq., 173 µl, 1.16 mmol), 2-mercaptoethanol (5eq. 135 µl, 1.93 mmol) in DMF. Washings were performed using DMF (3 x 30 ml), isopropanol (3-x 30 ml) followed by ethyl ether (3-x 30 ml) and the resin was dried under vacuum. The resulting N-MeTrp residue was subjected to three coupling cycles, one cycle

each with Fmoc-Arg (Pmc) (638 mg, 0.96 mmol), Fmoc-(D)Phe (373 mg, 0.96 mmol) and **Fmoc-Apc** (170 mg 0.96 mmol). The peptide resin was carried through steps 1 - 5 of protocol 1, washed with CH_2Cl_2 (three times) and treated with 300 µl valeric anhydride, 245 µl pyridine in 15 ml DMF for 5h. The resin was filtered and washed successively with 30 ml each of DMF (three times), isopropanol, CH_2Cl_2 (three times) and ethyl ether (3 times). The resulting pentyl-peptide resin was dried under vacuum and treated with 7 ml of 60 % trifluoroacetic acid in CH_2Cl_2, 1 % water and 615 ml triethylsilane (10 eq., 3.85 mmol) for 160 minutes. The resin was filtered off, washed with ~5-7 ml CH_2Cl_2, and the filtrates were concentrated on a Savant speed vacuum pump to yield the crude product.

This crude material was purified by preparative HPLC on a Vydac C18-column (2.5 x 20 cm) and eluted with a linear gradient of 10-60% B (buffer A: 0.1% TFA/H_2O, buffer B: 0.1% TFA/CH_3CN) in 60 min., flow rate 8ml/min, detection 280 nm. The main peak was cut by analytical HPLC analysis of collected fractions, pooled and lyophilized to yield 30 mg (~10 %) of a white, amorphous powder. This compound was homogeneous by HPLC. LR-Electrospray: $C_{47}H_{62}N_{10}O_6$, cal: 863 observed: m/z (864 M+H).

EXAMPLE 53

Penta-**Apc**-(D)Phe-Arg-**N-methylTrp**-NH_2

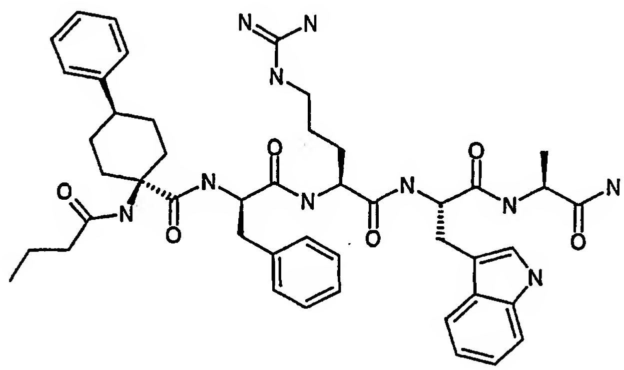


Fmoc-Linker-BHA resin (700 mg, 0.385 mmol) synthesized using the procedure in Example 29 was subjected to solid phase synthesis using DIC / HOBT coupling conditions and washings were performed as shown in the protocol 1. All amino acid couplings were performed using DIC (5 eq.), HOBT (2.5 eq.) as the coupling reagents and the Fmoc-amino acid (2.5 eq.) The resin was subjected to washing steps 1-6 as shown in protocol 1, after each peptide coupling. One coupling cycle was performed with Fmoc-Trp (461 mg, 0.96 mmol). After Fmoc removal from Trp residue, the resulting amine was converted to it's 2-nitrobenzene sulfonyl derivative using 2-nitrobenzenesulfonyl chloride (5 eq., 426 mg, 1.93 mmol) and DIPEA (5 eq.) as the base in DMF. Washings were performed using DMF, (6 x 30 ml) followed by CH_2Cl_2 (3 x 30 ml) and the resin was dried under vacuum. The sulfonamide obtained was subjected to methylation using triphenylphosphine (5 eq., 505 mg, 1.93 mmol), N, N-diethylazodicarboxylate (5 eq., 303 μl, 1.93 mmol) and methanol (10eq. 156 μl, 3.85 mmol) in THF. Washings were performed using THF (6 x 30 ml) followed by CH_2Cl_2 (5 x 30 ml) and the resin was dried under vacuum. The 2-nitrobenzene sulfonyl group was then removed using 1,8-diazabicyclo [5.4.0] undec-7-ene (3 eq., 173 μl, 1.16 mmol), 2-mercaptoethanol (5eq. 135 μl, 1.93 mmol) in DMF. Washings were performed using DMF (3 x 30 ml), isopropanol (3 x 30 ml) followed by ethyl ether (3 x 30 ml) and the resin was dried under vacuum. The resulting N-MeTrp residue was subjected to three coupling cycles, one cycle each with Fmoc-Arg (Pmc) (638 mg, 0.96 mmol), Fmoc- (D)Phe (373 mg, 0.96 mmol) and **Fmoc-Apc** (170 mg 0.96 mmol). The peptide resin was carried through steps 1 - 5 of protocol 1, washed with CH_2Cl_2 (three times) and treated with 300 μl valeric anhydride, 245 μl pyridine in 15 ml DMF for 5h. The resin was filtered and washed successively with 30 ml each of DMF (three times), isopropanol, CH_2Cl_2 (three times) and ethyl ether (3 times). The resulting pentyl-peptide resin was dried under vacuum and treated with 7 ml of 60 % trifluoroacetic acid in CH_2Cl_2, 1 % water and 615 ml triethylsilane (10 eq., 3.85 mmol) for 160 minutes. The resin was filtered off, washed with ~5-7 ml CH_2Cl_2, and the filtrates were concentrated on a Savant speed vacuum pump to yield the crude product.

This crude material was purified by preparative HPLC on a Vydac C18-column (2.5 x 20 cm) and eluted with a linear gradient of 10-60% B (buffer A: 0.1% TFA/H_2O, buffer B: 0.1% TFA/CH_3CN) in 60 min., flow rate 8ml/min, detection 280 nm . The main peak was cut by analytical HPLC analysis of collected fractions, pooled and lyophilized to yield 43 mg (14 %) of a white, amorphous powder. This compound was homogeneous by HPLC. LR-Electrospray: $C_{45}H_{59}N_9O_5$, cal: 806 observed: m/z (807 M+H).

EXAMPLE 54

Bu-Apc-(D)Phe-Arg-Trp-Ala-NH₂



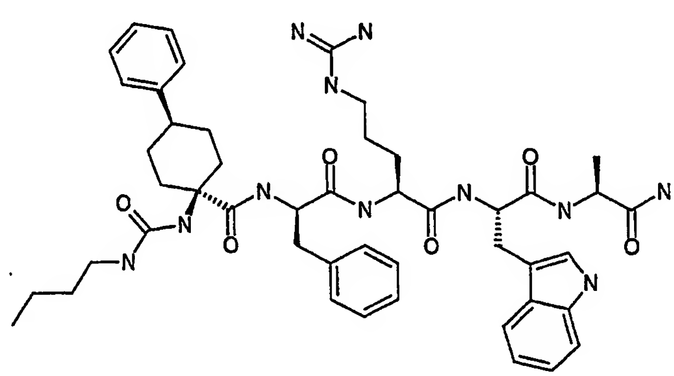
Fmoc-Linker-BHA resin (360 mg, 0.2 mmol) from Example 29 were subjected to solid phase synthesis using protocol 1 described above. All couplings were performed using HBTU in DMF as the coupling agent and DIPEA (3 equiv.) as base. Five coupling cycles were performed of one cycle each with **Fmoc-Ala** (187 mg, 0.6 mmol) and HBTU (226 mg, 0.6 mmol), Fmoc-Trp (260 mg, 0.6 mmol) and HBTU (226 mg, 0.6 mmol), Fmoc-Arg (Pmc) (400 mg, 0.6 mmol) and HBTU (226 mg, 0.6 mmol), Fmoc-(D)Phe (240 mg, 0.6 mmol) and HBTU (226 mg, 0.6 mmol), **Fmoc-Apc** (275 mg 0.6 mmol) and HBTU (226 mg, 0.6 mmol). The peptide resin was carried through steps 1 - 5 of protocol 1, washed with CH_2Cl_2 (three times) and treated with 1 mL butyric anhydride in 6% DIPEA/CH_2Cl_2 30 minutes. The resin was filtered and washed successively with 20 ml each of CH_2Cl_2 (two times), isopropanol, and CH_2Cl_2 (three times). The resin was dried under vacuum to yield 580 mg of butyl-Pentapeptide resin.

The butyl-Pentapeptide resin was treated with 40 µL ethanedithiol, 40 µL dimethylsulfide, 120 µL anisole, and 4 mL trifluoroacetic acid at room temperature for 180 min. The resin was filtered off, washed with ~2 ml TFA and the filtrates precipitated in chilled ethyl ether. The precipitates were centrifuged and the ether layer decanted. The residue was washed with two or three volumes of Et_2O and recentrifuged and the crude product was dried under vacuum to yield 145 mg of an off-white solid.

This crude material was purified by preparative HPLC on a Vydac C18-column (2.5 x 20 cm) and eluted with a linear gradient of 10-60% B (buffer A: 0.1% TFA/H_2O, buffer B: 0.1% TFA/CH_3CN) in 60 min., flow rate 8ml/min, detection 280 nm. The main peak was cut by analytical HPLC analysis of collected fractions, pooled and lyophilized to yield 61 mg (36 %) of a white, amorphous powder. This compound was homogeneous by HPLC. LR-Electrospray: $C_{46}H_{60}N_{10}O_6$, cal: 849 observed: m/z (850 M+H).

EXAMPLE 55

Bu-carbamoyl-Apc-(D)Phe-Arg-Trp-Ala-NH$_2$



Fmoc-Linker-BHA resin (360 mg, 0.2 mmol) from Example 29 were subjected to solid phase synthesis using protocol 1 described above. All couplings were performed using HBTU in DMF as the coupling agent and DIPEA (3 equiv.) as base. Five coupling cycles were performed of one cycle each with **Fmoc-Ala** (187 mg, 0.6 mmol) and HBTU (226 mg, 0.6 mmol), Fmoc-Trp (260 mg, 0.6 mmol) and HBTU (226 mg, 0.6 mmol), Fmoc-Arg (Pmc)

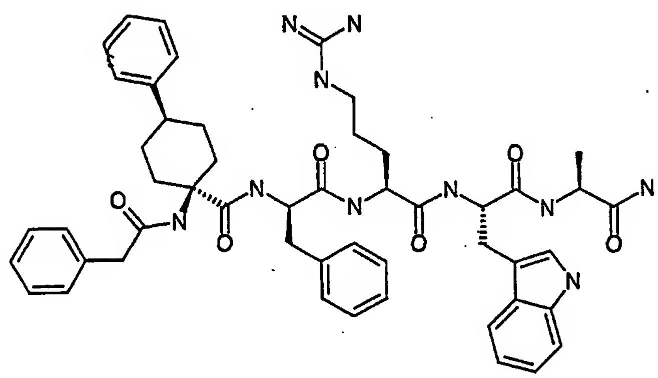
(400 mg, 0.6 mmol) and HBTU (226 mg, 0.6 mmol), Fmoc-(D)Phe (240 mg, 0.6 mmol) and HBTU (226 mg, 0.6 mmol), **Fmoc-Apc** (275 mg 0.6 mmol) and HBTU (226 mg, 0.6 mmol). The peptide resin was carried through steps 1 - 5 of protocol 1, washed with CH_2Cl_2 (three times) and treated with n-butyl isocyanate (5 equ.) in 6% DIPEA/CH_2Cl_2 for 30 minutes. The resin was filtered and washed successively with 20 ml each of CH_2Cl_2 (two times), isopropanol, and CH_2Cl_2 (three times). The resin was dried under vacuum to yield 600 mg of Bu-carbamoyl Pentapeptide resin.

The Bu-carbamoyl Pentapeptide resin was treated with 40 µL ethanedithiol, 40 µL dimethylsulfide, 120 µL anisole, and 4 mL trifluoroacetic acid at room temperature for 180 min. The resin was filtered off, washed with ~2 ml TFA and the filtrates precipitated in chilled ethyl ether. The precipitates were centrifuged and the ether layer decanted. The residue was washed with two or three volumes of Et_2O and recentrifuged and the crude product was dried under vacuum to yield 143 mg of an off-white solid.

This crude material was purified by preparative HPLC on a Vydac C18-column (2.5 x 20 cm) and eluted with a linear gradient of 10-60% B (buffer A: 0.1% TFA/H_2O, buffer B: 0.1% TFA/CH_3CN) in 60 min., flow rate 8ml/min, detection 280 nm. The main peak was cut by analytical HPLC analysis of collected fractions, pooled and lyophilized to yield 65 mg (37 %) of a white, amorphous powder. This compound was homogeneous by HPLC. LR-Electrospray: $C_{47}H_{63}N_{11}O_6$, cal: 878 observed: m/z (879 M+H).

EXAMPLE 56

Phenylacetyl-Apc-(D)Phe-Arg-Trp-Ala-NH_2



Fmoc-Linker-BHA resin (360 mg, 0.2 mmol) from Example 29 were subjected to solid phase synthesis using protocol 1 described above. All couplings were performed using HBTU in DMF as the coupling agent and DIPEA (3 equiv.) as base. Five coupling cycles were performed of one cycle each with **Fmoc-Ala** (187 mg, 0.6 mmol) and HBTU (226 mg, 0.6 mmol), Fmoc-Trp (260 mg, 0.6 mmol) and HBTU (226 mg, 0.6 mmol), Fmoc-Arg (Pmc) (400 mg, 0.6 mmol) and HBTU (226 mg, 0.6 mmol), Fmoc-(D)Phe (240 mg, 0.6 mmol) and HBTU (226 mg, 0.6 mmol), **Fmoc-Apc** (275 mg 0.6 mmol) and HBTU (226 mg, 0.6 mmol). The peptide resin was carried through steps 1 - 5 of protocol 1, washed with CH_2Cl_2 (three times) and treated with phenylacetic acid (82 mg, 0.6 mmol) and HBTU (226 mg, 0.6 mmol) in DMF. The resin was filtered and washed successively with 20 ml each of CH_2Cl_2 (two times), isopropanol, and CH_2Cl_2 (three times). The resin was dried under vacuum to yield 600 mg of phenylacetyl-Pentapeptide resin.

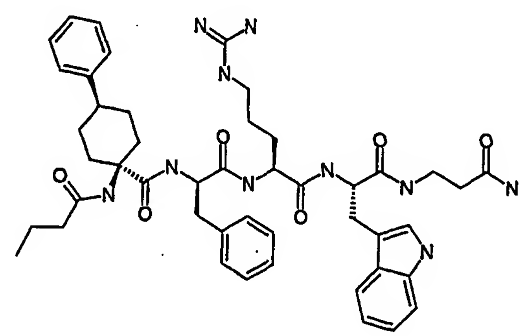
The phenylacetyl-Pentapeptide resin was treated with 40 µL ethanedithiol, 40 µL dimethylsulfide, 120 µL anisole, and 4 mL trifluoroacetic acid at room temperature for 180 min. The resin was filtered off, washed with ~2 ml TFA and the filtrates precipitated in chilled ethyl ether. The precipitates were centrifuged and the ether layer decanted. The

residue was washed with two or three volumes of Et_2O and recentrifuged and the crude product was dried under vacuum to yield 138 mg of an off-white solid.

This crude material was purified by preparative HPLC on a Vydac C18-column (2.5 x 20 cm) and eluted with a linear gradient of 10-60% B (buffer A: 0.1% TFA/H_2O, buffer B: 0.1% TFA/CH_3CN) in 60 min., flow rate 8ml/min, detection 280 nm. The main peak was cut by analytical HPLC analysis of collected fractions, pooled and lyophilized to yield 53 mg (30 %) of a white, amorphous powder. This compound was homogeneous by HPLC. LR-Electrospray: $C_{50}H_{60}N_{10}O_6$, cal: 897 observed: m/z (898 M+H).

EXAMPLE 57

Bu-Apc-(D)Phe-Arg-Trp-β-Ala-NH$_2$



Fmoc-Linker-BHA resin (360 mg, 0.2 mmol) from Example 29 were subjected to solid phase synthesis using protocol 1 described above. All couplings were performed using HBTU in DMF as the coupling agent and DIPEA (3 equiv.) as base. Five coupling cycles were performed of one cycle each with **Fmoc-β-Ala** (186 mg, 0.6 mal) and HBTU (226 mg, 0.6 mal), Fmoc-Trp (260 mg, 0.6 mmol) and HBTU (226 mg, 0.6 mmol), Fmoc-Arg (Pmc) (400 mg, 0.6 mmol) and HBTU (226 mg, 0.6 mmol), Fmoc-(D)Phe (240 mg, 0.6 mmol) and HBTU (226 mg, 0.6 mmol), **Fmoc-Apc** (275 mg 0.6 mmol) and HBTU (226 mg, 0.6 mmol). The peptide resin was carried through steps 1 - 5 of protocol 1, washed with CH_2Cl_2 (three times) and treated with butyric anhydride in 6% DIPEA/DMF for 12 hours.. The resin was filtered and washed successively with 20 ml each of CH_2Cl_2 (two times), isopropanol, and

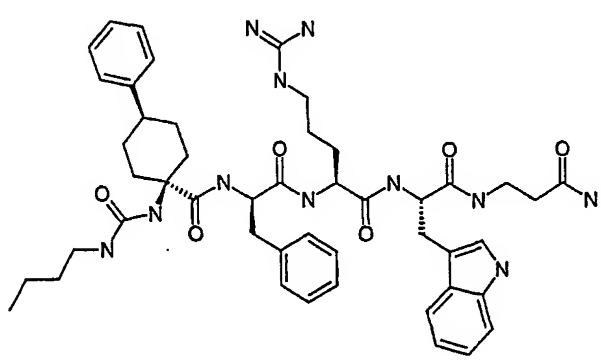
CH_2Cl_2 (three times). The resin was dried under vacuum to yield 550 mg of Butyl-Pentapeptide resin.

The Butyl-Pentapeptide resin was treated with 40 µL ethanedithiol, 40 µL dimethylsulfide, 120 µL anisole, and 4 mL trifluoroacetic acid at room temperature for 180 min. The resin was filtered off, washed with ~2 ml TFA and the filtrates precipitated in chilled ethyl ether. The precipitates were centrifuged and the ether layer decanted. The residue was washed with two or three volumes of Et_2O and recentrifuged and the crude product was dried under vacuum to yield 135 mg of an off-white solid.

This crude material was purified by preparative HPLC on a Vydac C18-column (2.5 x 20 cm) and eluted with a linear gradient of 10-60% B (buffer A: 0.1% TFA/H_2O, buffer B: 0.1% TFA/CH_3CN) in 60 min., flow rate 8ml/min, detection 280 nm. The main peak was cut by analytical HPLC analysis of collected fractions, pooled and lyophilized to yield 55 mg (32 %) of a white, amorphous powder. This compound was homogeneous by HPLC. LR-Electrospray: $C_{46}H_{60}N_{10}O_6$, cal: 848 observed: m/z (850 M+H).

EXAMPLE 58

Bu-Carbamoyl-Apc-(D)Phe-Arg-Trp-β-**Ala**-NH_2



Fmoc-Linker-BHA resin (360 mg, 0.2 mmol) from Example 29 were subjected to solid phase synthesis using protocol 1 described above. All couplings were performed using HBTU in DMF as the coupling agent and DIPEA (3 equiv.) as base. Five coupling cycles were

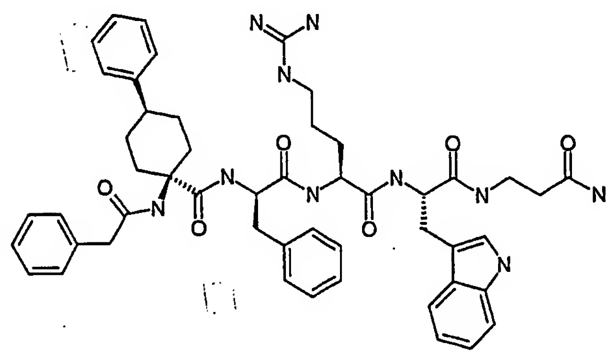
performed of one cycle each with **Fmoc-β-Ala** (186 mg, 0.6 mal) and HBTU (226 mg, 0.6 mal), Fmoc-Trp (260 mg, 0.6 mmol) and HBTU (226 mg, 0.6 mmol), Fmoc-Arg (Pmc) (400 mg, 0.6 mmol) and HBTU (226 mg, 0.6 mmol), Fmoc-(D)Phe (240 mg, 0.6 mmol) and HBTU (226 mg, 0.6 mmol), Fmoc-Apc (275 mg 0.6 mmol) and HBTU (226 mg, 0.6 mmol). The peptide resin was carried through steps 1 - 5 of protocol 1, washed with CH_2Cl_2 (three times) and treated n-butyl isocyanate (5eq) in 6% DIPEA/DMF for 12 hours. The resin was filtered and washed successively with 20 ml each of CH_2Cl_2 (two times), isopropanol, and CH_2Cl_2 (three times). The resin was dried under vacuum to yield 550 mg of Butyl carbamoyl-Pentapeptide resin.

The Butyl carbamoyl-Pentapeptide resin was treated with 40 μL ethanedithiol, 40 μL dimethylsulfide, 120 μL anisole, and 4 mL trifluoroacetic acid at room temperature for 180 min. The resin was filtered off, washed with ~2 ml TFA and the filtrates precipitated in chilled ethyl ether. The precipitates were centrifuged and the ether layer decanted. The residue was washed with two or three volumes of Et_2O and recentrifuged and the crude product was dried under vacuum to yield 135 mg of an off-white solid.

This crude material was purified by preparative HPLC on a Vydac C18-column (2.5 x 20 cm) and eluted with a linear gradient of 10-60% B (buffer A: 0.1% TFA/H_2O, buffer B: 0.1% TFA/CH_3CN) in 60 min., flow rate 8ml/min, detection 280 nm. The main peak was cut by analytical HPLC analysis of collected fractions, pooled and lyophilized to yield 55 mg (31 %) of a white, amorphous powder. This compound was homogeneous by HPLC. LR-Electrospray: $C_{47}H_{63}N_{11}O_6$, cal: 878 observed: m/z (879 M+H).

EXAMPLE 59

Phenylacetyl-Apc-(D)Phe-Arg-Trp-β-Ala-NH_2



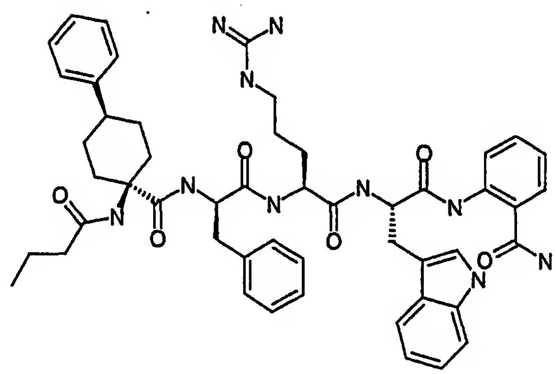
Fmoc-Linker-BHA resin (360 mg, 0.2 mmol) from Example 29 were subjected to solid phase synthesis using protocol 1 described above. All couplings were performed using HBTU in DMF as the coupling agent and DIPEA (3 equiv.) as base. Five coupling cycles were performed of one cycle each with **Fmoc-β-Ala** (186 mg, 0.6 mal) and HBTU (226 mg, 0.6 mal), Fmoc-Trp (260 mg, 0.6 mmol) and HBTU (226 mg, 0.6 mmol), Fmoc-Arg (Pmc) (400 mg, 0.6 mmol) and HBTU (226 mg, 0.6 mmol), Fmoc-(D)Phe (240 mg, 0.6 mmol) and HBTU (226 mg, 0.6 mmol), **Fmoc-Apc** (275 mg 0.6 mmol) and HBTU (226 mg, 0.6 mmol). The peptide resin was carried through steps 1 - 5 of protocol 1, washed with CH_2Cl_2 (three times) and treated with phenylacetic acid (82 mg, 0.6 mmol) and HBTU (226 mg, 0.6 mmol) in DMF. The resin was filtered and washed successively with 20 ml each of CH_2Cl_2 (two times), isopropanol, and CH_2Cl_2 (three times). The resin was dried under vacuum to yield 550 mg of phenylacetyl-Pentapeptide resin.

The phenylacetyl-Pentapeptide resin was treated with 40 μL ethanedithiol, 40 μL dimethylsulfide, 120 μL anisole, and 4 mL trifluoroacetic acid at room temperature for 180 min. The resin was filtered off, washed with ~2 ml TFA and the filtrates precipitated in chilled ethyl ether. The precipitates were centrifuged and the ether layer decanted. The residue was washed with two or three volumes of Et_2O and recentrifuged and the crude product was dried under vacuum to yield 129 mg of an off-white solid.

This crude material was purified by preparative HPLC on a Vydac C18-column (2.5 x 20 cm) and eluted with a linear gradient of 10-60% B (buffer A: 0.1% TFA/H_2O, buffer B: 0.1% TFA/CH_3CN) in 60 min., flow rate 8ml/min, detection 280 nm. The main peak was cut by analytical HPLC analysis of collected fractions, pooled and lyophilized to yield 49 mg (27 %) of a white, amorphous powder. This compound was homogeneous by HPLC. LR-Electrospray: $C_{50}H_{60}N_{10}O_6$, cal: 897 observed: m/z (898 M+H).

EXAMPLE 60

Bu-Apc-(D)Phe-Arg-Trp-2-Aba-NH$_2$



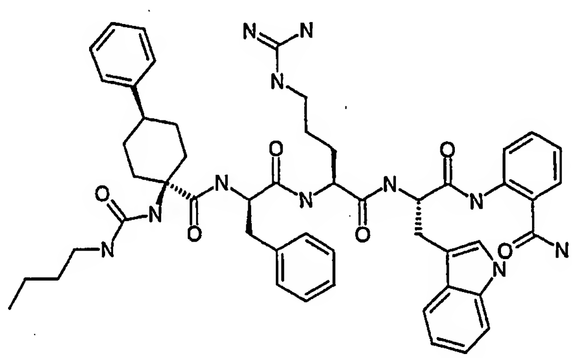
Fmoc-Linker-BHA resin (360 mg, 0.2 mmol) from Example 29 were subjected to solid phase synthesis using protocol 1 described above. All couplings were performed using HBTU in DMF as the coupling agent and DIPEA (3 equiv.) as base. Five coupling cycles were performed of one cycle each with **Fmoc-2-Aba** (215 mg, 0.6 mmol) and HBTU (226 mg, 0.6 mmol), Fmoc-Trp (260 mg, 0.6 mmol) and HBTU (226 mg, 0.6 mmol), Fmoc-Arg (Pmc) (400 mg, 0.6 mmol) and HBTU (226 mg, 0.6 mmol), Fmoc-(D)Phe (240 mg, 0.6 mmol) and HBTU (226 mg, 0.6 mmol), **Fmoc-Apc** (275 mg 0.6 mmol) and HBTU (226 mg, 0.6 mmol). The peptide resin was carried through steps 1 - 5 of protocol 1, washed with CH_2Cl_2 (three times) and treated with 1 mL butyric anhydride in 6% DIPEA/CH_2Cl_2 for 30 minutes. The resin was filtered and washed successively with 20 ml each of CH_2Cl_2 (two times), isopropanol, and CH_2Cl_2 (three times). The resin was dried under vacuum to yield 610 mg of butyl-Pentapeptide resin.

The butyl-Pentapeptide resin was treated with 40 µL ethanedithiol, 40 µL dimethylsulfide, 120 µL anisole, and 4 mL trifluoroacetic acid at room temperature for 180 min. The resin was filtered off, washed with ~2 ml TFA and the filtrates precipitated in chilled ethyl ether. The precipitates were centrifuged and the ether layer decanted. The residue was washed with two or three volumes of Et_2O and recentrifuged and the crude product was dried under vacuum to yield 140 mg of an off-white solid.

This crude material was purified by preparative HPLC on a Vydac C18-column (2.5 x 20 cm) and eluted with a linear gradient of 10-60% B (buffer A: 0.1% TFA/H_2O, buffer B: 0.1% TFA/CH_3CN) in 60 min., flow rate 8ml/min, detection 280 nm. The main peak was cut by analytical HPLC analysis of collected fractions, pooled and lyophilized to yield 47 mg (26 %) of a white, amorphous powder. This compound was homogeneous by HPLC. LR-Electrospray: $C_{50}H_{60}N_{10}O_6$, cal: 897 observed: m/z (898 M+H).

EXAMPLE 61

Bu-carbamoyl-Apc-(D)Phe-Arg-Trp-**2-Aba**-NH_2



Fmoc-Linker-BHA resin (360 mg, 0.2 mmol) from Example 29 were subjected to solid phase synthesis using protocol 1 described above. All couplings were performed using HBTU in DMF as the coupling agent and DIPEA (3 equiv.) as base. Five coupling cycles were performed of one cycle each with **Fmoc-2-Aba** (215 mg, 0.6 mmol) and HBTU (226 mg, 0.6 mmol), Fmoc-Trp (260 mg, 0.6 mmol) and HBTU (226 mg, 0.6 mmol), Fmoc-Arg (Pmc)

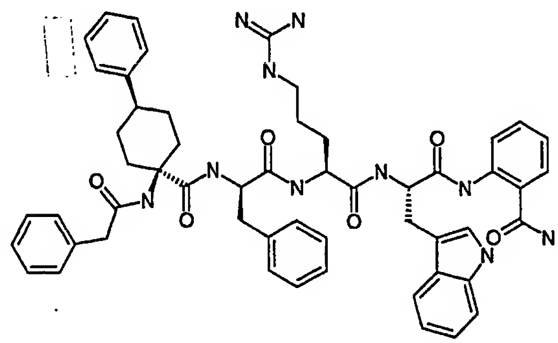
(400 mg, 0.6 mmol) and HBTU (226 mg, 0.6 mmol), Fmoc-(D)Phe (240 mg, 0.6 mmol) and HBTU (226 mg, 0.6 mmol), **Fmoc-Apc** (275 mg 0.6 mmol) and HBTU (226 mg, 0.6 mmol). The peptide resin was carried through steps 1 - 5 of protocol 1, washed with CH_2Cl_2 (three times) and treated with n-butyl isocyanate (5eq) in 6% DIPEA/CH_2Cl_2 30 minutes. The resin was filtered and washed successively with 20 ml each of CH_2Cl_2 (two times), isopropanol, and CH_2Cl_2 (three times). The resin was dried under vacuum to yield 610 mg of butyl-carbamoyl Pentapeptide resin.

The butyl-carbamoyl Pentapeptide resin was treated with 40 µL ethanedithiol, 40 µL dimethylsulfide, 120 µL anisole, and 4 mL trifluoroacetic acid at room temperature for 180 min. The resin was filtered off, washed with ~2 ml TFA and the filtrates precipitated in chilled ethyl ether. The precipitates were centrifuged and the ether layer decanted. The residue was washed with two or three volumes of Et_2O and recentrifuged and the crude product was dried under vacuum to yield 152 mg of an off-white solid.

This crude material was purified by preparative HPLC on a Vydac C18-column (2.5 x 20 cm) and eluted with a linear gradient of 10-60% B (buffer A: 0.1% TFA/H_2O, buffer B: 0.1% TFA/CH_3CN) in 60 min., flow rate 8ml/min, detection 280 nm. The main peak was cut by analytical HPLC analysis of collected fractions, pooled and lyophilized to yield 55 mg (30 %) of a white, amorphous powder. This compound was homogeneous by HPLC. LR-Electrospray: $C_{51}H_{63}N_{11}O_6$, cal: 926 observed: m/z (927 M+H).

EXAMPLE 62

Phenylacetyl-Apc-(D)Phe-Arg-Trp-2-Aba-NH$_2$



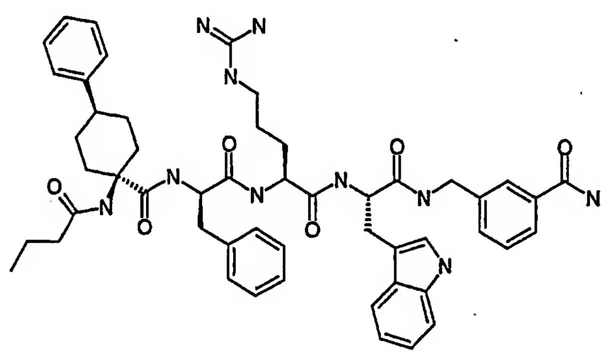
Fmoc-Linker-BHA resin (360 mg, 0.2 mmol) from Example 29 were subjected to solid phase synthesis using protocol 1 described above. All couplings were performed using HBTU in DMF as the coupling agent and DIPEA (3 equiv.) as base. Five coupling cycles were performed of one cycle each with **Fmoc-2-Aba** (215 mg, 0.6 mmol) and HBTU (226 mg, 0.6 mmol), Fmoc-Trp (260 mg, 0.6 mmol) and HBTU (226 mg, 0.6 mmol), Fmoc-Arg (Pmc) (400 mg, 0.6 mmol) and HBTU (226 mg, 0.6 mmol), Fmoc-(D)Phe (240 mg, 0.6 mmol) and HBTU (226 mg, 0.6 mmol), **Fmoc-Apc** (275 mg 0.6 mmol) and HBTU (226 mg, 0.6 mmol). The peptide resin was carried through steps 1 - 5 of protocol 1, washed with CH_2Cl_2 (three times) and treated with phenylacetic acid (82 mg, 0.6 mmol) and HBTU (226 mg, 0.6 mmol) in DMF. The resin was filtered and washed successively with 20 ml each of CH_2Cl_2 (two times), isopropanol, and CH_2Cl_2 (three times). The resin was dried under vacuum to yield 615 mg of phenylacetyl-Pentapeptide resin.

The phenylacetyl-Pentapeptide resin was treated with 40 µL ethanedithiol, 40 µL dimethylsulfide, 120 µL anisole, and 4 mL trifluoroacetic acid at room temperature for 180 min. The resin was filtered off, washed with ~2 ml TFA and the filtrates precipitated in chilled ethyl ether. The precipitates were centrifuged and the ether layer decanted. The residue was washed with two or three volumes of Et_2O and recentrifuged and the crude product was dried under vacuum to yield 142 mg of an off-white solid.

This crude material was purified by preparative HPLC on a Vydac C18-column (2.5 x 20 cm) and eluted with a linear gradient of 10-60% B (buffer A: 0.1% TFA/H_2O, buffer B: 0.1% TFA/CH_3CN) in 60 min., flow rate 8ml/min, detection 280 nm. The main peak was cut by analytical HPLC analysis of collected fractions, pooled and lyophilized to yield 53 mg (29 %) of a white, amorphous powder. This compound was homogeneous by HPLC. LR-Electrospray: $C_{54}H_{60}N_{10}O_6$, cal: 945 observed: m/z (955 M+H).

EXAMPLE 63

Bu-Apc-(D)Phe-Arg-Trp-3-Amb-NH_2



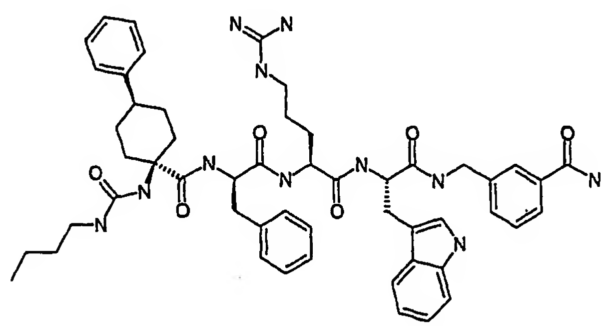
Fmoc-Linker-BHA resin (360 mg, 0.2 mmol) from Example 29 were subjected to solid phase synthesis using protocol 1 described above. All couplings were performed using HBTU in DMF as the coupling agent and DIPEA (3 equiv.) as base. Five coupling cycles were performed of one cycle each with **Fmoc-3-Amb** (230 mg, 0.6 mmol) and HBTU (226 mg, 0.6 mmol), Fmoc-Trp (260 mg, 0.6 mmol) and HBTU (226 mg, 0.6 mmol), Fmoc-Arg (Pmc) (400 mg, 0.6 mmol) and HBTU (226 mg, 0.6 mmol), Fmoc-(D)Phe (240 mg, 0.6 mmol) and HBTU (226 mg, 0.6 mmol), **Fmoc-Apc** (275 mg 0.6 mmol) and HBTU (226 mg, 0.6 mmol). The peptide resin was carried through steps 1 - 5 of protocol 1, washed with CH_2Cl_2 (three times) and treated with 1 mL of butyric anhydride in 6% DIPEA/CH_2Cl_2 for 30 minutes. The resin was filtered and washed successively with 20 ml each of CH_2Cl_2 (two times), isopropanol, and CH_2Cl_2 (three times). The resin was dried under vacuum to yield 590 mg of butyl-Pentapeptide resin.

The butyl-Pentapeptide resin was treated with 40 μL ethanedithiol, 40 μL dimethylsulfide, 120 μL anisole, and 4 mL trifluoroacetic acid at room temperature for 180 min. The resin was filtered off, washed with ~2 ml TFA and the filtrates precipitated in chilled ethyl ether. The precipitates were centrifuged and the ether layer decanted. The residue was washed with two or three volumes of Et_2O and recentrifuged and the crude product was dried under vacuum to yield 140 mg of an off-white solid.

This crude material was purified by preparative HPLC on a Vydac C18-column (2.5 x 20 cm) and eluted with a linear gradient of 10-60% B (buffer A: 0.1% TFA/H_2O, buffer B: 0.1% TFA/CH_3CN) in 60 min., flow rate 8ml/min, detection 280 nm. The main peak was cut by analytical HPLC analysis of collected fractions, pooled and lyophilized to yield 50 mg (27 %) of a white, amorphous powder. This compound was homogeneous by HPLC. LR-Electrospray: $C_{51}H_{62}N_{10}O_6$, cal: 911 observed: m/z (912 M+H).

EXAMPLE 64

Bu-carbamoyl-Apc-(D)Phe-Arg-Trp-3-Amb-NH_2



Fmoc-Linker-BHA resin (360 mg, 0.2 mmol) from Example 29 were subjected to solid phase synthesis using protocol 1 described above. All couplings were performed using HBTU in DMF as the coupling agent and DIPEA (3 equiv.) as base. Five coupling cycles were performed of one cycle each with **Fmoc-3-Amb** (230 mg, 0.6 mmol) and HBTU (226 mg, 0.6 mmol), Fmoc-Trp (260 mg, 0.6 mmol) and HBTU (226 mg, 0.6 mmol), Fmoc-Arg (Pmc) (400 mg, 0.6 mmol) and HBTU (226 mg, 0.6 mmol), Fmoc-(D)Phe (240 mg, 0.6 mmol) and

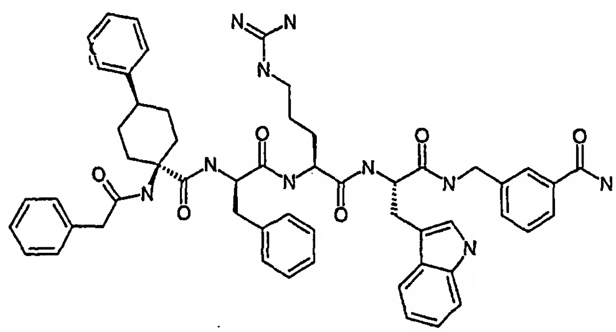
HBTU (226 mg, 0.6 mmol), **Fmoc-Apc** (275 mg 0.6 mmol) and HBTU (226 mg, 0.6 mmol). The peptide resin was carried through steps 1 - 5 of protocol 1, washed with CH_2Cl_2 (three times) and treated with n-butyl isocyanate (5eq) in 6% DIPEA/CH_2Cl_2 for 30 minutes. The resin was filtered and washed successively with 20 ml each of CH_2Cl_2 (two times), isopropanol, and CH_2Cl_2 (three times). The resin was dried under vacuum to yield 600 mg of butyl-carbamoyl Pentapeptide resin.

The butyl-carbamoyl Pentapeptide resin was treated with 40 µL ethanedithiol, 40 µL dimethylsulfide, 120 µL anisole, and 4 mL trifluoroacetic acid at room temperature for 180 min. The resin was filtered off, washed with ~2 ml TFA and the filtrates precipitated in chilled ethyl ether. The precipitates were centrifuged and the ether layer decanted. The residue was washed with two or three volumes of Et_2O and recentrifuged and the crude product was dried under vacuum to yield 143 mg of an off-white solid.

This crude material was purified by preparative HPLC on a Vydac C18-column (2.5 x 20 cm) and eluted with a linear gradient of 10-60% B (buffer A: 0.1% TFA/H_2O, buffer B: 0.1% TFA/CH_3CN) in 60 min., flow rate 8ml/min, detection 280 nm. The main peak was cut by analytical HPLC analysis of collected fractions, pooled and lyophilized to yield 53 mg (28 %) of a white, amorphous powder. This compound was homogeneous by HPLC. LR-Electrospray: $C_{52}H_{65}N_{11}O_6$, cal: 940 observed: m/z (941 M+H).

EXAMPLE 65

Phenylacetyl-Apc-(D)Phe-Arg-Trp-3-Amb-NH_2



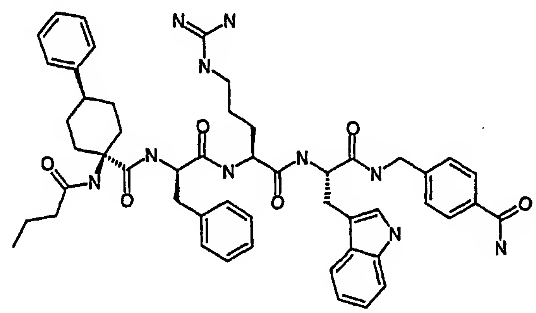
Fmoc-Linker-BHA resin (360 mg, 0.2 mmol) from Example 29 were subjected to solid phase synthesis using protocol 1 described above. All couplings were performed using HBTU in DMF as the coupling agent and DIPEA (3 equiv.) as base. Five coupling cycles were performed of one cycle each with **Fmoc-3-Amb** (230 mg, 0.6 mmol) and HBTU (226 mg, 0.6 mmol), Fmoc-Trp (260 mg, 0.6 mmol) and HBTU (226 mg, 0.6 mmol), Fmoc-Arg (Pmc) (400 mg, 0.6 mmol) and HBTU (226 mg, 0.6 mmol), Fmoc-(D)Phe (240 mg, 0.6 mmol) and HBTU (226 mg, 0.6 mmol), **Fmoc-Apc** (275 mg 0.6 mmol) and HBTU (226 mg, 0.6 mmol). The peptide resin was carried through steps 1 - 5 of protocol 1, washed with CH_2Cl_2 (three times) and treated with phenylacetic acid (82 mg, 0.6 mmol) and HBTU (226 mg, 0.6 mmol) in DMF. The resin was filtered and washed successively with 20 ml each of CH_2Cl_2 (two times), isopropanol, and CH_2Cl_2 (three times). The resin was dried under vacuum to yield 580 mg of phenylacetyl-Pentapeptide resin.

The phenylacetyl-Pentapeptide resin was treated with 40 µL ethanedithiol, 40 µL dimethylsulfide, 120 µL anisole, and 4 mL trifluoroacetic acid at room temperature for 180 min. The resin was filtered off, washed with ~2 ml TFA and the filtrates precipitated in chilled ethyl ether. The precipitates were centrifuged and the ether layer decanted. The residue was washed with two or three volumes of Et_2O and recentrifuged and the crude product was dried under vacuum to yield 135 mg of an off-white solid.

This crude material was purified by preparative HPLC on a Vydac C18-column (2.5 x 20 cm) and eluted with a linear gradient of 10-60% B (buffer A: 0.1% TFA/H_2O, buffer B: 0.1% TFA/CH_3CN) in 60 min., flow rate 8ml/min, detection 280 nm. The main peak was cut by analytical HPLC analysis of collected fractions, pooled and lyophilized to yield 49mg (26 %) of a white, amorphous powder. This compound was homogeneous by HPLC. LR-Electrospray: $C_{55}H_{62}N_{10}O_6$, cal: 959 observed: m/z (960 M+H).

EXAMPLE 66

Bu-Apc-(D)Phe-Arg-Trp-4-Amb-NH$_2$



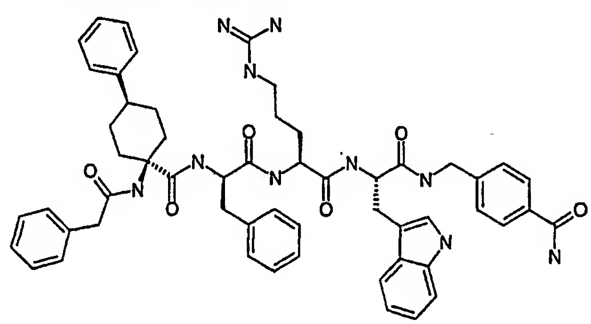
Fmoc-Linker-BHA resin (360 mg, 0.2 mmol) from Example 29 were subjected to solid phase synthesis using protocol 1 described above. All couplings were performed using HBTU in DMF as the coupling agent and DIPEA (3 equiv.) as base. Five coupling cycles were performed of one cycle each with **Fmoc-4-Amb** (230 mg, 0.6 mmol) and HBTU (226 mg, 0.6 mmol), Fmoc-Trp (260 mg, 0.6 mmol) and HBTU (226 mg, 0.6 mmol), Fmoc-Arg (Pmc) (400 mg, 0.6 mmol) and HBTU (226 mg, 0.6 mmol), Fmoc-(D)Phe (240 mg, 0.6 mmol) and HBTU (226 mg, 0.6 mmol), **Fmoc-Apc** (275 mg 0.6 mmol) and HBTU (226 mg, 0.6 mmol). The peptide resin was carried through steps 1 - 5 of protocol 1, washed with CH_2Cl_2 (three times) and treated with 1 mL butyric anhydride in 6% DIPEA/CH_2Cl_2 for 30 minutes. The resin was filtered and washed successively with 20 ml each of CH_2Cl_2 (two times), isopropanol, and CH_2Cl_2 (three times). The resin was dried under vacuum to yield 615 mg of butyl-Pentapeptide resin.

The butyl-Pentapeptide resin was treated with 40 μL ethanedithiol, 40 μL dimethylsulfide, 120 μL anisole, and 4 mL trifluoroacetic acid at room temperature for 180 min. The resin was filtered off, washed with ~2 ml TFA and the filtrates precipitated in chilled ethyl ether. The precipitates were centrifuged and the ether layer decanted. The residue was washed with two or three volumes of Et_2O and recentrifuged and the crude product was dried under vacuum to yield 153 mg of an off-white solid.

This crude material was purified by preparative HPLC on a Vydac C18-column (2.5 x 20 cm) and eluted with a linear gradient of 10-60% B (buffer A: 0.1% TFA/H_2O, buffer B: 0.1% TFA/CH_3CN) in 60 min., flow rate 8ml/min, detection 280 nm. The main peak was cut by analytical HPLC analysis of collected fractions, pooled and lyophilized to yield 55 mg (30 %) of a white, amorphous powder. This compound was homogeneous by HPLC. LR-Electrospray: $C_{51}H_{62}N_{10}O_6$, cal: 911 observed: m/z (912 M+H).

EXAMPLE 67

Phenylacetyl-Apc-(D)Phe-Arg-Trp-4-Amb-NH_2



Fmoc-Linker-BHA resin (360 mg, 0.2 mmol) from Example 29 were subjected to solid phase synthesis using protocol 1 described above. All couplings were performed using HBTU in DMF as the coupling agent and DIPEA (3 equiv.) as base. Five coupling cycles were performed of one cycle each with **Fmoc-4-Amb** (230 mg, 0.6 mmol) and HBTU (226 mg, 0.6 mmol), Fmoc-Trp (260 mg, 0.6 mmol) and HBTU (226 mg, 0.6 mmol), Fmoc-Arg (Pmc) (400 mg, 0.6 mmol) and HBTU (226 mg, 0.6 mmol), Fmoc-(D)Phe (240 mg, 0.6 mmol) and HBTU (226 mg, 0.6 mmol), **Fmoc-Apc** (275 mg 0.6 mmol) and HBTU (226 mg, 0.6 mmol).

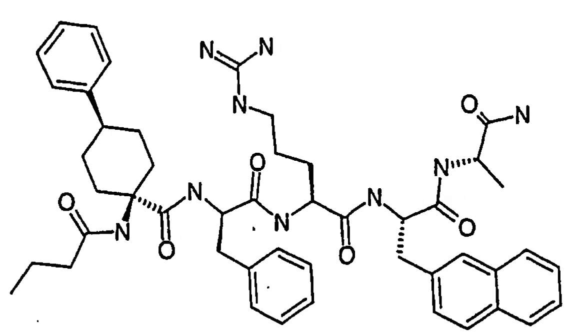
The peptide resin was carried through steps 1 - 5 of protocol 1, washed with CH_2Cl_2 (three times) and treated with phenylacetic acid (82 mg, 0.6 mmol) and HBTU (226 mg, 0.6 mmol) in DMF. The resin was filtered and washed successively with 20 ml each of CH_2Cl_2 (two times), isopropanol, and CH_2Cl_2 (three times). The resin was dried under vacuum to yield 585 mg of phenylacetyl-Pentapeptide resin.

The phenylacetyl-Pentapeptide resin was treated with 40 µL ethanedithiol, 40 µL dimethylsulfide, 120 µL anisole, and 4 mL trifluoroacetic acid at room temperature for 180 min. The resin was filtered off, washed with ~2 ml TFA and the filtrates precipitated in chilled ethyl ether. The precipitates were centrifuged and the ether layer decanted. The residue was washed with two or three volumes of Et_2O and recentrifuged and the crude product was dried under vacuum to yield 142 mg of an off-white solid.

This crude material was purified by preparative HPLC on a Vydac C18-column (2.5 x 20 cm) and eluted with a linear gradient of 10-60% B (buffer A: 0.1% TFA/H_2O, buffer B: 0.1% TFA/CH_3CN) in 60 min., flow rate 8ml/min, detection 280 nm. The main peak was cut by analytical HPLC analysis of collected fractions, pooled and lyophilized to yield 47 mg (26 %) of a white, amorphous powder. This compound was homogeneous by HPLC. LR-Electrospray: $C_{55}H_{62}N_{10}O_6$, cal: 959 observed: m/z (960 M+H).

EXAMPLE 68

Bu-Apc-(D)Phe-Arg-(2)Nal-Ala-NH_2



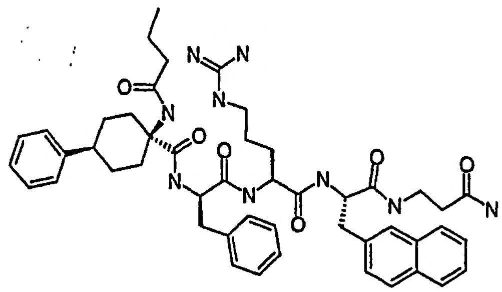
Fmoc-Linker-BHA resin (360 mg, 0.2 mmol) from Example 29 were subjected to solid phase synthesis using protocol 1 described above. All couplings were performed using HBTU in DMF as the coupling agent and DIPEA (3 equiv.) as base. Five coupling cycles were performed of one cycle each with **Fmoc-Ala** (187 mg, 0.6 mmol) and HBTU (226 mg, 0.6 mmol), Fmoc-(2)Nal (265 mg, 0.6 mmol) and HBTU (226 mg, 0.6 mmol), Fmoc-Arg (Pmc) (400 mg, 0.6 mmol) and HBTU (226 mg, 0.6 mmol), Fmoc-(D)Phe (240 mg, 0.6 mmol) and HBTU (226 mg, 0.6 mmol), **Fmoc-Apc** (275 mg 0.6 mmol) and HBTU (226 mg, 0.6 mmol). The peptide resin was carried through steps 1 - 5 of protocol 1, washed with CH_2Cl_2 (three times) and treated with 1 mL of butyric anhydride in 6% DIPEA/CH_2Cl_2 for 30 minutes. The resin was filtered and washed successively with 20 ml each of CH_2Cl_2 (two times), isopropanol, and CH_2Cl_2 (three times). The resin was dried under vacuum to yield 610 mg of Butyl Pentapeptide resin.

The butyl-Pentapeptide resin was treated with 40 μL ethanedithiol, 40 μL dimethylsulfide, 120 μL anisole, and 4 mL trifluoroacetic acid at room temperature for 180 min. The resin was filtered off, washed with ~2 ml TFA and the filtrates precipitated in chilled ethyl ether. The precipitates were centrifuged and the ether layer decanted. The residue was washed with two or three volumes of Et_2O and recentrifuged and the crude product was dried under vacuum to yield 149 mg of an off-white solid.

This crude material was purified by preparative HPLC on a Vydac C18-column (2.5 x 20 cm) and eluted with a linear gradient of 10-60% B (buffer A: 0.1% TFA/H_2O, buffer B: 0.1% TFA/CH_3CN) in 60 min., flow rate 8ml/min, detection 280 nm. The main peak was cut by analytical HPLC analysis of collected fractions, pooled and lyophilized to yield 57 mg (33 %) of a white, amorphous powder. This compound was homogeneous by HPLC. LR-Electrospray: $C_{48}H_{61}N_9O_6$, cal 860 observed: m/z (861 M+H).

EXAMPLE 69

Bu-Apc-(D)Phe-Arg-(2)Nal-beta-Ala-NH_2



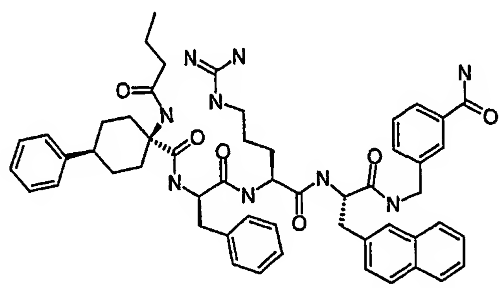
Fmoc-Linker-BHA resin (360 mg, 0.2 mmol) from Example 29 were subjected to solid phase synthesis using protocol 1 described above. All couplings were performed using HBTU in DMF as the coupling agent and DIPEA (3 equiv.) as base. Five coupling cycles were performed of one cycle each with **Fmoc-beta-Ala** (187 mg, 0.6 mmol) and HBTU (226 mg, 0.6 mmol), Fmoc-(2)Nal (265 mg, 0.6 mmol) and HBTU (226 mg, 0.6 mmol), Fmoc-Arg (Pmc) (400 mg, 0.6 mmol) and HBTU (226 mg, 0.6 mmol), Fmoc-(D)Phe (240 mg, 0.6 mmol) and HBTU (226 mg, 0.6 mmol), **Fmoc-Apc** (275 mg 0.6 mmol) and HBTU (226 mg, 0.6 mmol). The peptide resin was carried through steps 1 - 5 of protocol 1, washed with CH_2Cl_2 (three times) and treated with 1 mL Butyric anhydride in 6% DIPEA/CH_2Cl_2 for 30 minutes. The resin was filtered and washed successively with 20 ml each of CH_2Cl_2 (two times), isopropanol, and CH_2Cl_2 (three times). The resin was dried under vacuum to yield 605 mg of Butyl Pentapeptide resin.

The butyl-Pentapeptide resin was treated with 40 µL ethanedithiol, 40 µL dimethylsulfide, 120 µL anisole, and 4 mL trifluoroacetic acid at room temperature for 180 min. The resin was filtered off, washed with ~2 ml TFA and the filtrates precipitated in chilled ethyl ether. The precipitates were centrifuged and the ether layer decanted. The residue was washed with two or three volumes of Et_2O and recentrifuged and the crude product was dried under vacuum to yield 142 mg of an off-white solid.

This crude material was purified by preparative HPLC on a Vydac C18-column (2.5 x 20 cm) and eluted with a linear gradient of 10-60% B (buffer A: 0.1% TFA/H_2O, buffer B: 0.1% TFA/CH_3CN) in 60 min., flow rate 8ml/min, detection 280 nm. The main peak was cut by analytical HPLC analysis of collected fractions, pooled and lyophilized to yield 54 mg (32 %) of a white, amorphous powder. This compound was homogeneous by HPLC. LR-Electrospray: $C_{48}H_{61}N_9O_6$, cal 860 observed: m/z (861 M+H).

EXAMPLE 70

Bu-Apc-(D)Phe-Arg-(2)Nal-**3-Amb**-NH_2



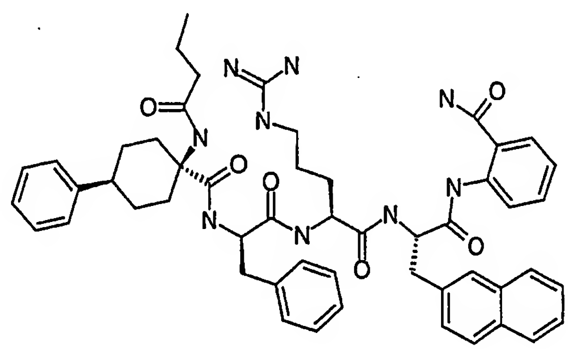
Fmoc-Linker-BHA resin (360 mg, 0.2 mmol) from Example 29 were subjected to solid phase synthesis using protocol 1 described above. All couplings were performed using HBTU in DMF as the coupling agent and DIPEA (3 equiv.) as base. Five coupling cycles were performed of one cycle each with **Fmoc-3- Amb** (230 mg, 0.6 mmol) and HBTU (226 mg, 0.6 mmol), Fmoc-(2)Nal (265 mg, 0.6 mmol) and HBTU (226 mg, 0.6 mmol), Fmoc-Arg (Pmc) (400 mg, 0.6 mmol) and HBTU (226 mg, 0.6 mmol), Fmoc-(D)Phe (240 mg, 0.6 mmol) and HBTU (226 mg, 0.6 mmol), **Fmoc-Apc** (275 mg 0.6 mmol) and HBTU (226 mg, 0.6 mmol). The peptide resin was carried through steps 1 - 5 of protocol 1, washed with CH_2Cl_2 (three times) and treated with 1 mL Butyric anhydride in 6% DIPEA/CH_2Cl_2 for 30 minutes. The resin was filtered and washed successively with 20 ml each of CH_2Cl_2 (two times), isopropanol, and CH_2Cl_2 (three times). The resin was dried under vacuum to yield 550 mg of Butyl Pentapeptide resin.

The butyl-Pentapeptide resin was treated with 40 μL ethanedithiol, 40 μL dimethylsulfide, 120 μL anisole, and 4 mL trifluoroacetic acid at room temperature for 180 min. The resin was filtered off, washed with ~2 ml TFA and the filtrates precipitated in chilled ethyl ether. The precipitates were centrifuged and the ether layer decanted. The residue was washed with two or three volumes of Et_2O and recentrifuged and the crude product was dried under vacuum to yield 125 mg of an off-white solid.

This crude material was purified by preparative HPLC on a Vydac C18-column (2.5 x 20 cm) and eluted with a linear gradient of 10-60% B (buffer A: 0.1% TFA/H_2O, buffer B: 0.1% TFA/CH_3CN) in 60 min., flow rate 8ml/min, detection 280 nm. The main peak was cut by analytical HPLC analysis of collected fractions, pooled and lyophilized to yield 44 mg (27 %) of a white, amorphous powder. This compound was homogeneous by HPLC. LR-Electrospray: $C_{53}H_{63}N_9O_6$, cal 922 observed: m/z (923 M+H).

EXAMPLE 71

Bu-Apc-(D)Phe-Arg-(2)Nal-2-Aba-NH_2



Fmoc-Linker-BHA resin (360 mg, 0.2 mmol) from Example 29 were subjected to solid phase synthesis using protocol 1 described above. All couplings were performed using HBTU in DMF as the coupling agent and DIPEA (3 equiv.) as base. Five coupling cycles were performed of one cycle each with **Fmoc-2-Aba** (215 mg, 0.6 mmol) and HBTU (226 mg, 0.6 mmol), Fmoc-(2)Nal (265 mg, 0.6 mmol) and HBTU (226 mg, 0.6 mmol), Fmoc-Arg

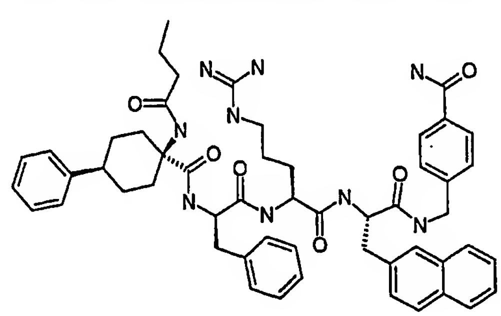
(Pmc) (400 mg, 0.6 mmol) and HBTU (226 mg, 0.6 mmol), Fmoc-(D)Phe (240 mg, 0.6 mmol) and HBTU (226 mg, 0.6 mmol), **Fmoc-Apc** (275 mg 0.6 mmol) and HBTU (226 mg, 0.6 mmol). The peptide resin was carried through steps 1 - 5 of protocol 1, washed with CH_2Cl_2 (three times) and treated with 1 mL butyric anhydride in 6% DIPEA/CH_2Cl_2 for 30 minutes. The resin was filtered and washed successively with 20 ml each of CH_2Cl_2 (two times), isopropanol, and CH_2Cl_2 (three times). The resin was dried under vacuum to yield 510 mg of Butyl Pentapeptide resin.

The butyl-Pentapeptide resin was treated with 40 μL ethanedithiol, 40 μL dimethylsulfide, 120 μL anisole, and 4 mL trifluoroacetic acid at room temperature for 180 min. The resin was filtered off, washed with ~2 ml TFA and the filtrates precipitated in chilled ethyl ether. The precipitates were centrifuged and the ether layer decanted. The residue was washed with two or three volumes of Et_2O and recentrifuged and the crude product was dried under vacuum to yield 114 mg of an off-white solid.

This crude material was purified by preparative HPLC on a Vydac C18-column (2.5 x 20 cm) and eluted with a linear gradient of 10-60% B (buffer A: 0.1% TFA/H_2O, buffer B: 0.1% TFA/CH_3CN) in 60 min., flow rate 8ml/min, detection 280 nm. The main peak was cut by analytical HPLC analysis of collected fractions, pooled and lyophilized to yield 36 mg (20 %) of a white, amorphous powder. This compound was homogeneous by HPLC. LR-Electrospray: $C_{52}H_{61}N_9O_6$, cal 908 observed: m/z (909 M+H).

EXAMPLE 72

Bu-Apc-(D)Phe-Arg-(2)Nal-4-Amb-NH$_2$



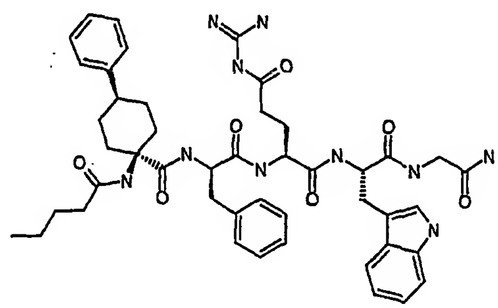
Fmoc-Linker-BHA resin (360 mg, 0.2 mmol) from Example 29 were subjected to solid phase synthesis using protocol 1 described above. All couplings were performed using HBTU in DMF as the coupling agent and DIPEA (3 equiv.) as base. Five coupling cycles were performed of one cycle each with **Fmoc-4- Amb** (230 mg, 0.6 mmol) and HBTU (226 mg, 0.6 mmol), Fmoc-(2)Nal (265 mg, 0.6 mmol) and HBTU (226 mg, 0.6 mmol), Fmoc-Arg (Pmc) (400 mg, 0.6 mmol) and HBTU (226 mg, 0.6 mmol), Fmoc-(D)Phe (240 mg, 0.6 mmol) and HBTU (226 mg, 0.6 mmol), **Fmoc-Apc** (275 mg 0.6 mmol) and HBTU (226 mg, 0.6 mmol). The peptide resin was carried through steps 1 - 5 of protocol 1, washed with CH_2Cl_2 (three times) and treated with 1 mL butyric anhydride in 6% DIPEA/CH_2Cl_2 for 30 minutes. The resin was filtered and washed successively with 20 ml each of CH_2Cl_2 (two times), isopropanol, and CH_2Cl_2 (three times). The resin was dried under vacuum to yield 620 mg of Butyl Pentapeptide resin.

The butyl-Pentapeptide resin was treated with 40 µL ethanedithiol, 40 µL dimethylsulfide, 120 µL anisole, and 4 mL trifluoroacetic acid at room temperature for 180 min. The resin was filtered off, washed with ~2 ml TFA and the filtrates precipitated in chilled ethyl ether. The precipitates were centrifuged and the ether layer decanted. The residue was washed with two or three volumes of Et_2O and recentrifuged and the crude product was dried under vacuum to yield 139 mg of an off-white solid.

This crude material was purified by preparative HPLC on a Vydac C18-column (2.5 x 20 cm) and eluted with a linear gradient of 10-60% B (buffer A: 0.1% TFA/H_2O, buffer B: 0.1% TFA/CH_3CN) in 60 min., flow rate 8ml/min, detection 280 nm. The main peak was cut by analytical HPLC analysis of collected fractions, pooled and lyophilized to yield 56 mg (31 %) of a white, amorphous powder. This compound was homogeneous by HPLC. LR-Electrospray: $C_{53}H_{63}N_9O_6$, cal 922 observed: m/z (923 M+H).

EXAMPLE 73

Penta-Apc-(D)Phe-acylguanidine-Trp-Gly-NH_2



Fmoc-Linker-BHA resin (360 mg, 0.2 mmol) from Example 29 were subjected to solid phase synthesis using protocol 1 described above. All couplings were performed using HBTU in DMF as the coupling agent and DIPEA (3 equiv.) as base. Five coupling cycles were performed of one cycle each with Fmoc-Gly (180 mg, 0.6 mmol) and HBTU (226 mg, 0.6 mmol), Fmoc-Trp (260 mg, 0.6 mmol) and HBTU (226 mg, 0.6 mmol), **Fmoc-Glu(allyl)** (250 mg, 0.6 mmol) and HBTU (226 mg, 0.6 mmol), Fmoc-(D)Phe (240 mg, 0.6 mmol) and HBTU (226 mg, 0.6 mmol), **Fmoc-Apc** (275 mg 0.6 mmol) and HBTU (226 mg, 0.6 mmol). The peptide resin was carried through steps 1 - 5 of protocol 1, washed with CH_2Cl_2 (three times) and treated with 1 mL valeric anhydride in 6% DIPEA/CH_2Cl_2 for 30 minutes. The resin was filtered and washed successively with 20 ml each of CH_2Cl_2 (two times), isopropanol, and CH_2Cl_2 (three times). The resin was dried under vacuum to yield Pentyl-Pentapeptide resin.

The allyl protecting group was removed using $PdCl_2$/Triphenylphosphine/tributyltin hydride under Argon in DMF. The guanidinylation was achieved using **Boc-Guanidine. HCl** (100mg, 0.6 mmol) and HBTU (226 mg, 0.6 mmol).

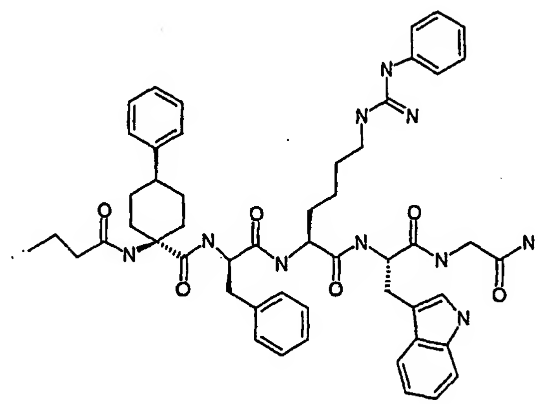
The Pentyl-Pentapeptide resin was treated with 40 µL ethanedithiol, 40 µL dimethylsulfide, 120 µL anisole, and 4 mL trifluoroacetic acid at room temperature for 180 min. The resin was filtered off, washed with ~2 ml TFA and the filtrates precipitated in chilled ethyl ether.

The precipitates were centrifuged and the ether layer decanted. The residue was washed with two or three volumes of Et_2O and recentrifuged and the crude product was dried under vacuum to yield 140 mg of an off-white solid.

This crude material was purified by preparative HPLC on a Vydac C18-column (2.5 x 20 cm) and eluted with a linear gradient of 10-60% B (buffer A: 0.1% TFA/H_2O, buffer B: 0.1% TFA/CH_3CN) in 60 min., flow rate 8ml/min, detection 280 nm. The main peak was cut by analytical HPLC analysis of collected fractions, pooled and lyophilized to yield 30 mg (15 %) of a white, amorphous powder. This compound was homogeneous by HPLC. LR-Electrospray: $C_{46}H_{58}N_{10}O_7$, cal 977 observed: m/z (978 M+H).

EXAMPLE 74

Bu-Apc-(D)Phe-**PhenylhomoArg**-Trp-Gly-NH2



Fmoc-Linker-BHA resin (360 mg, 0.2 mmol) from Example 29 were subjected to solid phase synthesis using protocol 1 described above. All couplings were performed using HBTU in DMF as the coupling agent and DIPEA (3 equiv.) as base. Five coupling cycles were performed of one cycle each with Fmoc-Gly (180 mg, 0.6 mmol) and HBTU (226 mg, 0.6 mmol), Fmoc-Trp (260 mg, 0.6 mmol) and HBTU (226 mg, 0.6 mmol), **Fmoc-Phenyl homo Arg** (295 mg, 0.6 mmol) and HBTU (226 mg, 0.6 mmol), Fmoc-(D)Phe (240 mg, 0.6 mmol) and HBTU (226 mg, 0.6 mmol), **Fmoc-Apc** (275 mg 0.6 mmol) and HBTU (226 mg, 0.6

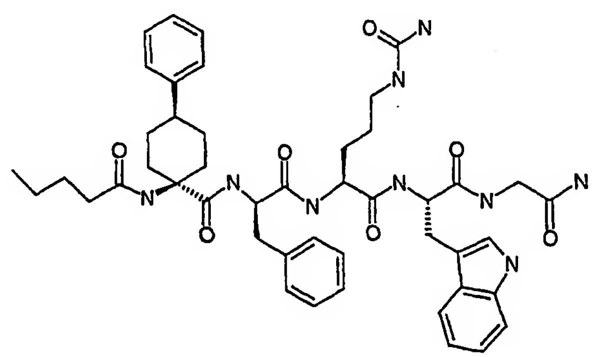
mmol). The peptide resin was carried through steps 1 - 5 of protocol 1, washed with CH_2Cl_2 (three times) and treated with 1 mL butyric anhydride in 6% DIPEA/CH_2Cl_2 for 30 minutes. The resin was filtered and washed successively with 20 ml each of CH_2Cl_2 (two times), isopropanol, and CH_2Cl_2 (three times). The resin was dried under vacuum to yield 570 mg of Butyl-Pentapeptide resin.

The Butyl-Pentapeptide resin was treated with 40 μL ethanedithiol, 40 μL dimethylsulfide, 120 μL anisole, and 4 mL trifluoroacetic acid at room temperature for 180 min. The resin was filtered off, washed with ~2 ml TFA and the filtrates precipitated in chilled ethyl ether. The precipitates were centrifuged and the ether layer decanted. The residue was washed with two or three volumes of Et_2O and recentrifuged and the crude product was dried under vacuum to yield 140 mg of an off-white solid.

This crude material was purified by preparative HPLC on a Vydac C18-column (2.5 x 20 cm) and eluted with a linear gradient of 10-60% B (buffer A: 0.1% TFA/H_2O, buffer B: 0.1% TFA/CH_3CN) in 60 min., flow rate 8ml/min, detection 280 nm. The main peak was cut by analytical HPLC analysis of collected fractions, pooled and lyophilized to yield 54 mg (30 %) of a white, amorphous powder. This compound was homogeneous by HPLC. LR-Electrospray: $C_{52}H_{64}N_{10}O_6$, cal 925 observed: m/z (926 M+H).

EXAMPLE 75

Penta-Apc-(D)Phe-Cit-Trp-Gly-NH_2



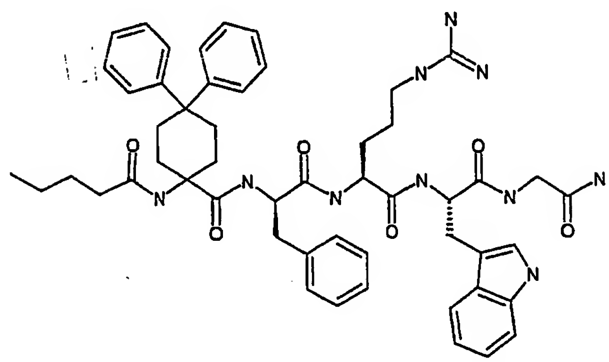
Fmoc-Linker-BHA resin (360 mg, 0.2 mmol) from Example 29 were subjected to solid phase synthesis using protocol 1 described above. All couplings were performed using HBTU in DMF as the coupling agent and DIPEA (3 equiv.) as base. Five coupling cycles were performed of one cycle each with Fmoc-Gly (180 mg, 0.6 mmol) and HBTU (226 mg, 0.6 mmol), Fmoc-Trp (260 mg, 0.6 mmol) and HBTU (226 mg, 0.6 mmol), **Fmoc-Cit** (240 mg, 0.6 mmol) and HBTU (226 mg, 0.6 mmol), Fmoc-(D)Phe (240 mg, 0.6 mmol) and HBTU (226 mg, 0.6 mmol), Fmoc-Apc (275 mg 0.6 mmol) and HBTU (226 mg, 0.6 mmol). The peptide resin was carried through steps 1 - 5 of protocol 1, washed with CH_2Cl_2 (three times) and treated with 1 mL valeric anhydride in 6% DIPEA/CH_2Cl_2 for 30 minutes. The resin was filtered and washed successively with 20 ml each of CH_2Cl_2 (two times), isopropanol, and CH_2Cl_2 (three times). The resin was dried under vacuum to yield 590 mg of Pentyl-Pentapeptide resin.

The Pentyl-Pentapeptide resin was treated with 40 μL ethanedithiol, 40 μL dimethylsulfide, 120 μL anisole, and 4 mL trifluoroacetic acid at room temperature for 180 min. The resin was filtered off, washed with ~2 ml TFA and the filtrates precipitated in chilled ethyl ether. The precipitates were centrifuged and the ether layer decanted. The residue was washed with two or three volumes of Et_2O and recentrifuged and the crude product was dried under vacuum to yield 152 mg of an off-white solid.

This crude material was purified by preparative HPLC on a Vydac C18-column (2.5 x 20 cm) and eluted with a linear gradient of 10-60% B (buffer A: 0.1% TFA/H_2O, buffer B: 0.1% TFA/CH_3CN) in 60 min., flow rate 8ml/min, detection 280 nm. The main peak was cut by analytical HPLC analysis of collected fractions, pooled and lyophilized to yield 65 mg (38 %) of a white, amorphous powder. This compound was homogeneous by HPLC. LR-Electrospray: $C_{46}H_{56}N_9O_7$, cal: 850 observed: m/z (851 M+H).

EXAMPLE 76

Penta-Adpc-(D)Phe-Arg-Trp-Gly-NH_2



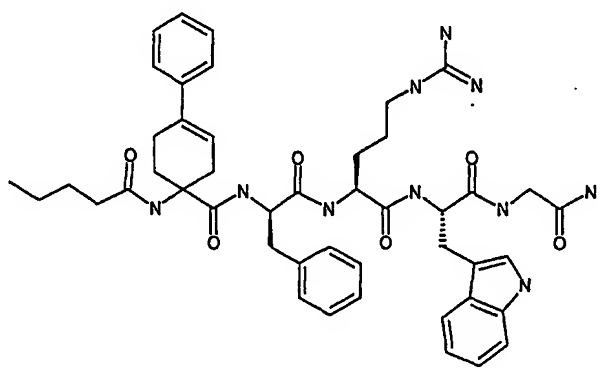
Fmoc-Linker-BHA resin (360 mg, 0.2 mmol) from Example 29 were subjected to solid phase synthesis using protocol 1 described above. All couplings were performed using HBTU in DMF as the coupling agent and DIPEA (3 equiv.) as base. Five coupling cycles were performed of one cycle each with Fmoc-Gly (180 mg, 0.6 mmol) and HBTU (226 mg, 0.6 mmol), Fmoc-Trp (260 mg, 0.6 mmol) and HBTU (226 mg, 0.6 mmol), Fmoc-Arg (Pmc) (400 mg, 0.6 mmol) and HBTU (226 mg, 0.6 mmol), Fmoc-(D)Phe (240 mg, 0.6 mmol) and HBTU (226 mg, 0.6 mmol), **Fmoc-Adpc** (320 mg 0.6 mmol) and HBTU (226 mg, 0.6 mmol). The peptide resin was carried through steps 1 - 5 of protocol 1, washed with CH_2Cl_2 (three times) and treated with 1 mL valeric anhydride in 6% DIPEA/CH_2Cl_2 for 30 minutes. The resin was filtered and washed successively with 20 ml each of CH_2Cl_2 (two times), isopropanol, and CH_2Cl_2 (three times). The resin was dried under vacuum to yield 610 mg of Pentyl-Pentapeptide resin.

The Pentyl-Pentapeptide resin was treated with 40 μL ethanedithiol, 40 μL dimethylsulfide, 120 μL anisole, and 4 mL trifluoroacetic acid at room temperature for 180 min. The resin was filtered off, washed with ~2 ml TFA and the filtrates precipitated in chilled ethyl ether. The precipitates were centrifuged and the ether layer decanted. The residue was washed with two or three volumes of Et_2O and recentrifuged and the crude product was dried under vacuum to yield 142 mg of an off-white solid.

This crude material was purified by preparative HPLC on a Vydac C18-column (2.5 x 20 cm) and eluted with a linear gradient of 10-60% B (buffer A: 0.1% TFA/H_2O, buffer B: 0.1% TFA/CH_3CN) in 60 min., flow rate 8ml/min, detection 280 nm. The main peak was cut by analytical HPLC analysis of collected fractions, pooled and lyophilized to yield 47 mg (26 %) of a white, amorphous powder. This compound was homogeneous by HPLC. LR-Electrospray: $C_{52}H_{64}N_{10}O_6$, cal: 925 observed: m/z (926 M+H).

EXAMPLE 77

Penta-Ape-(D)Phe-Arg-Trp-Gly-NH_2 (peak 1)



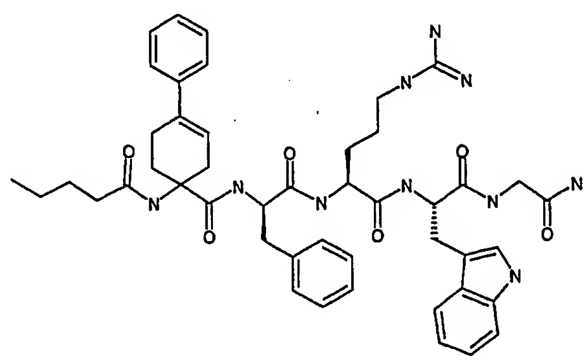
Fmoc-Linker-BHA resin (360 mg, 0.2 mmol) from Example 29 were subjected to solid phase synthesis using protocol 1 described above. All couplings were performed using HBTU in DMF as the coupling agent and DIPEA (3 equiv.) as base. Five coupling cycles were performed of one cycle each with Fmoc-Gly (180 mg, 0.6 mmol) and HBTU (226 mg, 0.6 mmol), Fmoc-Trp (260 mg, 0.6 mmol) and HBTU (226 mg, 0.6 mmol), Fmoc-Arg (Pmc) (400 mg, 0.6 mmol) and HBTU (226 mg, 0.6 mmol), Fmoc-(D)Phe (240 mg, 0.6 mmol) and HBTU (226 mg, 0.6 mmol), **Fmoc-Ape** (275 mg 0.6 mmol) and HBTU (226 mg, 0.6 mmol). The peptide resin was carried through steps 1 - 5 of protocol 1, washed with CH_2Cl_2 (three times) and treated with 1 mL valeric anhydride in 6% DIPEA/CH_2Cl_2 for 30 minutes. The resin was filtered and washed successively with 20 ml each of CH_2Cl_2 (two times), isopropanol, and CH_2Cl_2 (three times). The resin was dried under vacuum to yield 610 mg of Pentyl-Pentapeptide resin.

The Pentyl-Pentapeptide resin was treated with 40 µL ethanedithiol, 40 µL dimethylsulfide, 120 µL anisole, and 4 mL trifluoroacetic acid at room temperature for 180 min. The resin was filtered off, washed with ~2 ml TFA and the filtrates precipitated in chilled ethyl ether. The precipitates were centrifuged and the ether layer decanted. The residue was washed with two or three volumes of Et_2O and recentrifuged and the crude product was dried under vacuum to yield 140 mg of an off-white solid.

This crude material was purified by preparative HPLC on a Vydac C18-column (2.5 x 20 cm) and eluted with a linear gradient of 10-60% B (buffer A: 0.1% TFA/H_2O, buffer B: 0.1% TFA/CH_3CN) in 60 min., flow rate 8ml/min, detection 280 nm. The first main peak was cut by analytical HPLC analysis of collected fractions, pooled and lyophilized to yield 25 mg (15 %) of a white, amorphous powder. This compound was homogeneous by HPLC. LR-Electrospray: $C_{46}H_{58}N_{10}O_6$, cal: 847 observed: m/z (948 M+H).

EXAMPLE 78

Penta-Ape-(D)Phe-Arg-Trp-Gly-NH_2 (peak 2)



Fmoc-Linker-BHA resin (360 mg, 0.2 mmol) from Example 29 were subjected to solid phase synthesis using protocol 1 described above. All couplings were performed using HBTU in DMF as the coupling agent and DIPEA (3 equiv.) as base. Five coupling cycles were performed of one cycle each with Fmoc-Gly (180 mg, 0.6 mmol) and HBTU (226 mg, 0.6 mmol), Fmoc-Trp (260 mg, 0.6 mmol) and HBTU (226 mg, 0.6 mmol), Fmoc-Arg (Pmc)

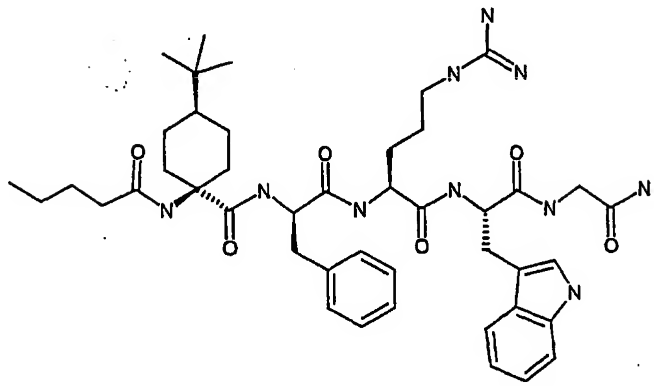
(400 mg, 0.6 mmol) and HBTU (226 mg, 0.6 mmol), Fmoc-(D)Phe (240 mg, 0.6 mmol) and HBTU (226 mg, 0.6 mmol), **Fmoc-Ape** (275 mg 0.6 mmol) and HBTU (226 mg, 0.6 mmol). The peptide resin was carried through steps 1 - 5 of protocol 1, washed with CH_2Cl_2 (three times) and treated with 1 mL valeric anhydride in 6% DIPEA/CH_2Cl_2 for 30 minutes. The resin was filtered and washed successively with 20 ml each of CH_2Cl_2 (two times), isopropanol, and CH_2Cl_2 (three times). The resin was dried under vacuum to yield 610 mg of Pentyl-Pentapeptide resin.

The Pentyl-Pentapeptide resin was treated with 40 µL ethanedithiol, 40 µL dimethylsulfide, 120 µL anisole, and 4 mL trifluoroacetic acid at room temperature for 180 min. The resin was filtered off, washed with ~2 ml TFA and the filtrates precipitated in chilled ethyl ether. The precipitates were centrifuged and the ether layer decanted. The residue was washed with two or three volumes of Et_2O and recentrifuged and the crude product was dried under vacuum to yield 140 mg of an off-white solid.

This crude material was purified by preparative HPLC on a Vydac C18-column (2.5 x 20 cm) and eluted with a linear gradient of 10-60% B (buffer A: 0.1% TFA/H_2O, buffer B: 0.1% TFA/CH_3CN) in 60 min., flow rate 8ml/min, detection 280 nm. The **second** main peak was cut by analytical HPLC analysis of collected fractions, pooled and lyophilized to yield 22 mg (14 %) of a white, amorphous powder. This compound was homogeneous by HPLC. LR-Electrospray: $C_{46}H_{58}N_{10}O_6$, cal: 847 observed: m/z (948 M+H).

EXAMPLE 79

Penta-Abc-(D)Phe-Arg-Trp-Gly-NH_2



Fmoc-Linker-BHA resin (360 mg, 0.2 mmol) from Example 29 were subjected to solid phase synthesis using protocol 1 described above. All couplings were performed using HBTU in DMF as the coupling agent and DIPEA (3 equiv.) as base. Five coupling cycles were performed of one cycle each with Fmoc-Gly (180 mg, 0.6 mmol) and HBTU (226 mg, 0.6 mmol), Fmoc-Trp (260 mg, 0.6 mmol) and HBTU (226 mg, 0.6 mmol), Fmoc-Arg (Pmc) (400 mg, 0.6 mmol) and HBTU (226 mg, 0.6 mmol), Fmoc-(D)Phe (240 mg, 0.6 mmol) and HBTU (226 mg, 0.6 mmol), **Fmoc-Abc** (270 mg 0.6 mmol) and HBTU (226 mg, 0.6 mmol). The peptide resin was carried through steps 1 - 5 of protocol 1, washed with CH_2Cl_2 (three times) and treated with 1 mL valeric anhydride in 6% DIPEA/CH_2Cl_2 for 30 minutes. The resin was filtered and washed successively with 20 ml each of CH_2Cl_2 (two times), isopropanol, and CH_2Cl_2 (three times). The resin was dried under vacuum to yield 580 mg of Pentyl-Pentapeptide resin.

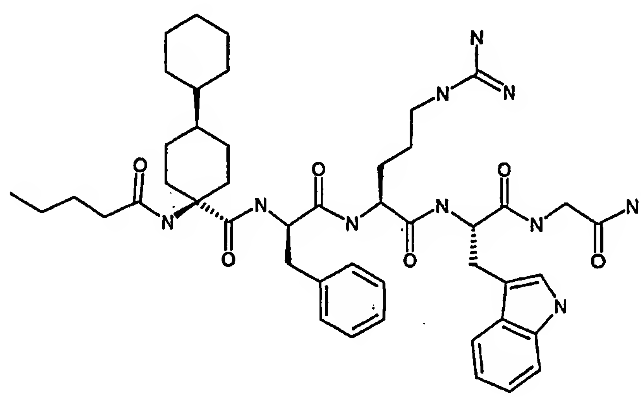
The Pentyl-Pentapeptide resin was treated with 40 μL ethanedithiol, 40 μL dimethylsulfide, 120 μL anisole, and 4 mL trifluoroacetic acid at room temperature for 180 min. The resin was filtered off, washed with ~2 ml TFA, and the filtrates precipitated in chilled ethyl ether. The precipitates were centrifuged and the ether layer decanted. The

residue was washed with two or three volumes of Et_2O and recentrifuged and the crude product was dried under vacuum to yield 155 mg of an off-white solid.

This crude material was purified by preparative HPLC on a Vydac C18-column (2.5 x 20 cm) and eluted with a linear gradient of 10-60% B (buffer A: 0.1% TFA/H_2O, buffer B: 0.1% TFA/CH_3CN) in 60 min., flow rate 8ml/min, detection 280 nm . The main peak was cut by analytical HPLC analysis of collected fractions, pooled and lyophilized to yield 61 mg (36 %) of a white, amorphous powder. This compound was homogeneous by HPLC. LR-Electrospray: $C_{44}H_{64}N_{10}O_6$, cal: 829 observed: m/z (830 M+H).

EXAMPLE 80

Penta-**Achc**-(D)Phe-Arg-Trp-Gly-NH_2



Fmoc-Linker-BHA resin (360 mg, 0.2 mmol) from Example 29 were subjected to solid phase synthesis using protocol 1 described above. All couplings were performed using HBTU in DMF as the coupling agent and DIPEA (3 equiv.) as base. Five coupling cycles were performed of one cycle each with Fmoc-Gly (180 mg, 0.6 mmol) and HBTU (226 mg, 0.6 mmol), Fmoc-Trp (260 mg, 0.6 mmol) and HBTU (226 mg, 0.6 mmol), Fmoc-Arg (Pmc) (400 mg, 0.6 mmol) and HBTU (226 mg, 0.6 mmol), Fmoc-(D)Phe (240 mg, 0.6 mmol) and HBTU (226 mg, 0.6 mmol), **Fmoc-Achc** (278 mg 0.6 mmol) and HBTU (226 mg, 0.6 mmol). The peptide resin was carried through steps 1 - 5 of protocol 1, washed with CH_2Cl_2

(three times) and treated with 1 mL valeric anhydride in 6% DIPEA/CH_2Cl_2 for 30 minutes. The resin was filtered and washed successively with 20 ml each of CH_2Cl_2 (two times), isopropanol, and CH_2Cl_2 (three times). The resin was dried under vacuum to yield 580 mg of Pentyl-Pentapeptide resin.

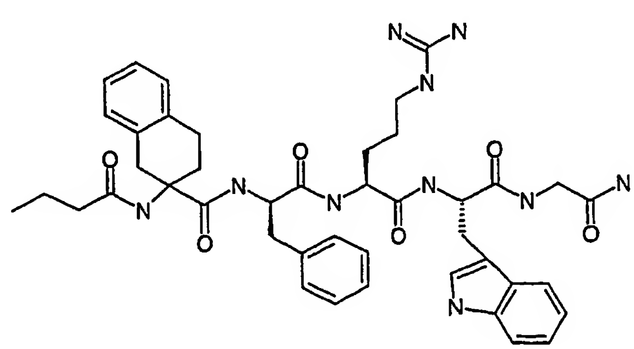
The Pentyl-Pentapeptide resin was treated with 40 µL ethanedithiol, 40 µL dimethylsulfide, 120 µL anisole, and 4 mL trifluoroacetic acid at room temperature for 180 min. The resin was filtered off, washed with ~2 ml TFA and the filtrates precipitated in chilled ethyl ether. The precipitates were centrifuged and the ether layer decanted. The residue was washed with two or three volumes of Et_2O and recentrifuged and the crude product was dried under vacuum to yield 145 mg of an off-white solid.

This crude material was purified by preparative HPLC on a Vydac C18-column (2.5 x 20 cm) and eluted with a linear gradient of 10-60% B (buffer A: 0.1% TFA/H_2O, buffer B: 0.1% TFA/CH_3CN) in 60 min., flow rate 8ml/min, detection 280 nm. The main peak was cut by analytical HPLC analysis of collected fractions, pooled and lyophilized to yield 65 mg (38 %) of a white, amorphous powder. This compound was homogeneous by HPLC. LR-Electrospray: $C_{46}H_{66}N_{10}O_6$, cal: 855 observed: m/z (856 M+H).

EXAMPLE 81

Preparation of

Bu-Atc-(D)Phe-Arg-Trp-Gly-NH_2



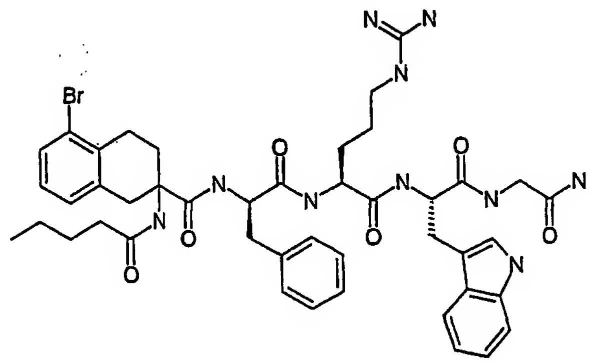
Fmoc-Linker-BHA resin (360 mg, 0.2 mmol) from Example 29 were subjected to solid phase synthesis using Protocol 1 above. All couplings were performed using HBTU in DMF as the coupling agent and DIPEA (3 equiv.) as base. Five coupling cycles were performed of one cycle each with Fmoc-Gly (180 mg, 0.6 mmol) and HBTU (226 mg, 0.6 mmol), Fmoc-Trp (260 mg, 0.6 mmol) and HBTU (226 mg, 0.6 mmol), Fmoc-Arg (Pmc) (400 mg, 0.6 mmol) and HBTU (226 mg, 0.6 mmol), Fmoc-(D)Phe (240 mg, 0.6 mmol) and HBTU (226 mg, 0.6 mmol), **Fmoc-(D,L)Atc** (252 mg 0.6 mmol) and HBTU (226 mg, 0.6 mmol). The peptide resin was carried through steps 1 - 5 of protocol 1, washed with CH_2Cl_2 (three times) and treated with 1 mL butyric anhydride in 6% DIPEA/CH_2Cl_2 for 30 minutes. The resin was filtered and washed successively with 20 ml each of CH_2Cl_2 (two times), isopropanol, and CH_2Cl_2 (three times). The resin was dried under vacuum to yield 550 mg of Bu-Pentapeptide resin.

The Bu-Pentapeptide resin was treated with 40 µL ethanedithiol, 40 µL dimethylsulfide, 120 µL anisole, and 4 mL trifluoroacetic acid at room temperature for 180 min. The resin was filtered off, washed with ~2 ml TFA and the filtrates precipitated in chilled ethyl ether. The precipitates were centrifuged and the ether layer decanted. The residue was washed with two or three volumes of Et_2O and recentrifuged and the crude product was dried under vacuum to yield 110 mg of an off-white solid.

This crude material was purified by preparative HPLC on a Vydac C18-column (2.5 x 20 cm) and eluted with a linear gradient of 10-60% B (buffer A: 0.1% TFA/H_2O, buffer B: 0.1% TFA/CH_3CN) in 60 min., flow rate 8ml/min, detection 280 nm. The **second** main peak was cut by analytical HPLC analysis of collected fractions, pooled and lyophilized to yield 42 mg (26 %) of a white, amorphous powder. This compound was homogeneous by HPLC. LR-Electrospray: $C_{43}H_{54}N_{10}O_6$, cal 807 observed: m/z (808 M+H).

EXAMPLE 82

Penta-5-**Br-(D,L)Atc**-(D)Phe-Arg-Trp-Gly-NH_2



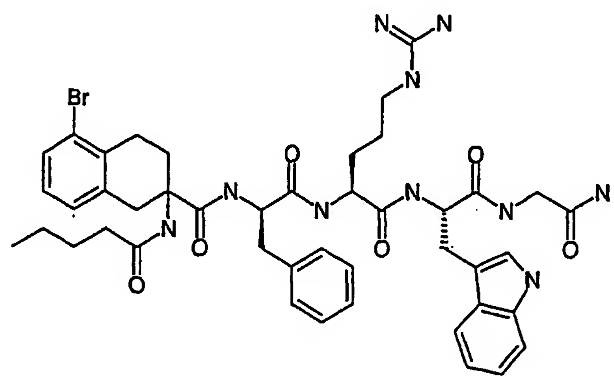
Fmoc-Linker-BHA resin (360 mg, 0.2 mmol) from Example 29 were subjected to solid phase synthesis using protocol 1 described above. All couplings were performed using HBTU in DMF as the coupling agent and DIPEA (3 equiv.) as base. Five coupling cycles were performed of one cycle each with Fmoc-Gly (180 mg, 0.6 mmol) and HBTU (226 mg, 0.6 mmol), Fmoc-Trp (260 mg, 0.6 mmol) and HBTU (226 mg, 0.6 mmol), Fmoc-Arg (Pmc) (400 mg, 0.6 mmol) and HBTU (226 mg, 0.6 mmol), Fmoc-(D)Phe (240 mg, 0.6 mmol) and HBTU (226 mg, 0.6 mmol), **Fmoc-5-Br-(D,L)Atc** (310 mg 0.6 mmol) and HBTU (226 mg, 0.6 mmol). The peptide resin was carried through steps 1 - 5 of protocol 1, washed with CH_2Cl_2 (three times) and treated with 1 mL valeric anhydride in 6% DIPEA/CH_2Cl_2 for 30 minutes. The resin was filtered and washed successively with 20 ml each of CH_2Cl_2 (two times), isopropanol, and CH_2Cl_2 (three times). The resin was dried under vacuum to yield 600 mg of Pentyl-Pentapeptide resin.

The Pentyl-Pentapeptide resin was treated with 40 μL ethanedithiol, 40 μL dimethylsulfide, 120 μL anisole, and 4 mL trifluoroacetic acid at room temperature for 180 min. The resin was filtered off, washed with ~2 ml TFA and the filtrates precipitated in chilled ethyl ether. The precipitates were centrifuged and the ether layer decanted. The residue was washed with two or three volumes of Et_2O and recentrifuged and the crude product was dried under vacuum to yield 135 mg of an off-white solid.

This crude material was purified by preparative HPLC on a Vydac C18-column (2.5 x 20 cm) and eluted with a linear gradient of 10-60% B (buffer A: 0.1% TFA/H_2O, buffer B: 0.1% TFA/CH_3CN) in 60 min., flow rate 8ml/min, detection 280 nm. The main peak was cut by analytical HPLC analysis of collected fractions, pooled and lyophilized to yield 45 mg (25 %) of a white, amorphous powder. This compound was homogeneous by HPLC. LR-Electrospray: $C_{44}H_{55}N_{10}O_6Br$, cal 900 observed: m/z (901 M+H).

EXAMPLE 83

Penta-**5-Br-Atc**-(D)Phe-Arg-Trp-Gly-NH_2 (peak 1)



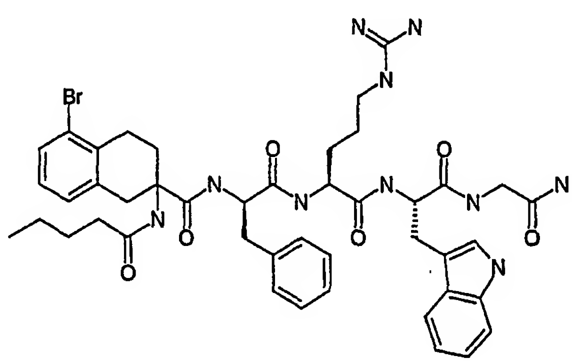
Fmoc-Linker-BHA resin (360 mg, 0.2 mmol) from Example 29 were subjected to solid phase synthesis using protocol 1 described above. All couplings were performed using HBTU in DMF as the coupling agent and DIPEA (3 equiv.) as base. Five coupling cycles were performed of one cycle each with Fmoc-Gly (180 mg, 0.6 mmol) and HBTU (226 mg, 0.6 mmol), Fmoc-Trp (260 mg, 0.6 mmol) and HBTU (226 mg, 0.6 mmol), Fmoc-Arg (Pmc) (400 mg, 0.6 mmol) and HBTU (226 mg, 0.6 mmol), Fmoc-(D)Phe (240 mg, 0.6 mmol) and HBTU (226 mg, 0.6 mmol), **Fmoc-(D,L)5-BrAtc** (310 mg 0.6 mmol) and HBTU (226 mg, 0.6 mmol). The peptide resin was carried through steps 1 - 5 of protocol 1, washed with CH_2Cl_2 (three times) and treated with 1 mL valeric anhydride in 6% DIPEA/CH_2Cl_2 for 30 minutes. The resin was filtered and washed successively with 20 ml each of CH_2Cl_2 (two times), isopropanol, and CH_2Cl_2 (three times). The resin was dried under vacuum to yield 590 mg of Pentyl-Pentapeptide resin.

The Pentyl-Pentapeptide resin was treated with 40 µL ethanedithiol, 40 µL dimethylsulfide, 120 µL anisole, and 4 mL trifluoroacetic acid at room temperature for 180 min. The resin was filtered off, washed with ~2 ml TFA and the filtrates precipitated in chilled ethyl ether. The precipitates were centrifuged and the ether layer decanted. The residue was washed with two or three volumes of Et_2O and recentrifuged and the crude product was dried under vacuum to yield 130 mg of an off-white solid.

This crude material was purified by preparative HPLC on a Vydac C18-column (2.5 x 20 cm) and eluted with a linear gradient of 10-60% B (buffer A: 0.1% TFA/H_2O, buffer B: 0.1% TFA/CH_3CN) in 60 min., flow rate 8ml/min, detection 280 nm. The first main peak was cut by analytical HPLC analysis of collected fractions, pooled and lyophilized to yield 40 mg (22 %) of a white, amorphous powder. This compound was homogeneous by HPLC. LR-Electrospray: $C_{44}H_{55}N_{10}O_6Br$, cal 900 observed: m/z (901 M+H).

EXAMPLE 84

Penta-5-BrAtc-(D)Phe-Arg-Trp-Gly-NH_2 (peak 2)



Fmoc-Linker-BHA resin (360 mg, 0.2 mmol) from Example 29 were subjected to solid phase synthesis using protocol 1 described above. All couplings were performed using HBTU in DMF as the coupling agent and DIPEA (3 equiv.) as base. Five coupling cycles were performed of one cycle each with Fmoc-Gly (180 mg, 0.6 mmol) and HBTU (226 mg, 0.6 mmol), Fmoc-Trp (260 mg, 0.6 mmol) and HBTU (226 mg, 0.6 mmol), Fmoc-Arg (Pmc) (400 mg, 0.6 mmol) and HBTU (226 mg, 0.6 mmol), Fmoc-(D)Phe (240 mg, 0.6 mmol) and

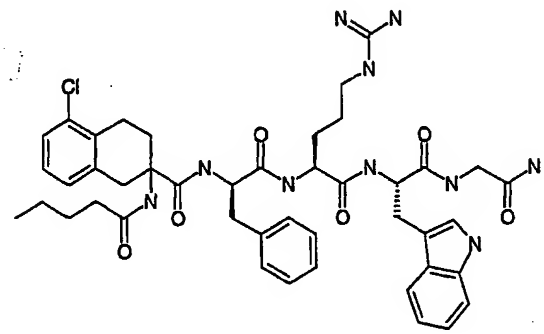
HBTU (226 mg, 0.6 mmol), **Fmoc-(D,L)-5-BrAtc** (310 mg 0.6 mmol) and HBTU (226 mg, 0.6 mmol). The peptide resin was carried through steps 1 - 5 of protocol 1, washed with CH_2Cl_2 (three times) and treated with 1 mL valeric anhydride in 6% DIPEA/CH_2Cl_2 for 30 minutes. The resin was filtered and washed successively with 20 ml each of CH_2Cl_2 (two times), isopropanol, and CH_2Cl_2 (three times). The resin was dried under vacuum to yield 580 mg of Pentyl-Pentapeptide resin.

The Pentyl-Pentapeptide resin was treated with 40 μL ethanedithiol, 40 μL dimethylsulfide, 120 μL anisole, and 4 mL trifluoroacetic acid at room temperature for 180 min. The resin was filtered off, washed with ~2 ml TFA and the filtrates precipitated in chilled ethyl ether. The precipitates were centrifuged and the ether layer decanted. The residue was washed with two or three volumes of Et_2O and recentrifuged and the crude product was dried under vacuum to yield 145 mg of an off-white solid.

This crude material was purified by preparative HPLC on a Vydac C18-column (2.5 x 20 cm) and eluted with a linear gradient of 10-60% B (buffer A: 0.1% TFA/H_2O, buffer B: 0.1% TFA/CH_3CN) in 60 min., flow rate 8ml/min, detection 280 nm. The **second** main peak was cut by analytical HPLC analysis of collected fractions, pooled and lyophilized to yield 55 mg (30%) of a white, amorphous powder. This compound was homogeneous by HPLC. LR-Electrospray: $C_{44}H_{55}N_{10}O_6Br$, cal 900 observed: m/z (901 M+H).

EXAMPLE 85

Penta-5-Cl-(D,L)Atc-(D)Phe-Arg-Trp-Gly-NH_2



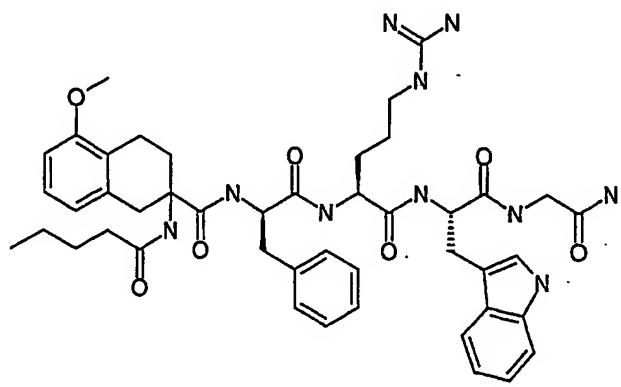
Fmoc-Linker-BHA resin (360 mg, 0.2 mmol) from Example 29 were subjected to solid phase synthesis using protocol 1 described above. All couplings were performed using HBTU in DMF as the coupling agent and DIPEA (3 equiv.) as base. Five coupling cycles were performed of one cycle each with Fmoc-Gly (180 mg, 0.6 mmol) and HBTU (226 mg, 0.6 mmol), Fmoc-Trp (260 mg, 0.6 mmol) and HBTU (226 mg, 0.6 mmol), Fmoc-Arg (Pmc) (400 mg, 0.6 mmol) and HBTU (226 mg, 0.6 mmol), Fmoc-(D)Phe (240 mg, 0.6 mmol) and HBTU (226 mg, 0.6 mmol), **Fmoc-5-ClAtc** (290 mg 0.6 mmol) and HBTU (226 mg, 0.6 mmol). The peptide resin was carried through steps 1 - 5 of protocol 1, washed with CH_2Cl_2 (three times) and treated with 1 mL valeric anhydride in 6% DIPEA/CH_2Cl_2 for 30 minutes. The resin was filtered and washed successively with 20 ml each of CH_2Cl_2 (two times), isopropanol, and CH_2Cl_2 (three times). The resin was dried under vacuum to yield 620 mg of Pentyl-Pentapeptide resin.

The Pentyl-Pentapeptide resin was treated with 40 µL ethanedithiol, 40 µL dimethylsulfide, 120 µL anisole, and 4 mL trifluoroacetic acid at room temperature for 180 min. The resin was filtered off, washed with ~2 ml TFA and the filtrates precipitated in chilled ethyl ether. The precipitates were centrifuged and the ether layer decanted. The residue was washed with two or three volumes of Et_2O and recentrifuged and the crude product was dried under vacuum to yield 150 mg of an off-white solid.

This crude material was purified by preparative HPLC on a Vydac C18-column (2.5 x 20 cm) and eluted with a linear gradient of 10-60% B (buffer A: 0.1% TFA/H_2O, buffer B: 0.1% TFA/CH_3CN) in 60 min., flow rate 8ml/min, detection 280 nm. The main peak was cut by analytical HPLC analysis of collected fractions, pooled and lyophilized to yield 48 mg (28 %) of a white, amorphous powder. This compound was homogeneous by HPLC. LR-Electrospray: $C_{44}H_{55}N_{10}O_6Cl$, cal 855 observed: m/z (856 M+H).

EXAMPLE 86

Penta-5-MeO-(D,L)Atc-(D)Phe-Arg-Trp-Gly -NH_2



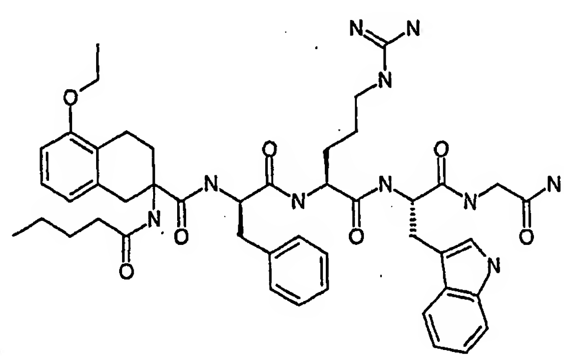
Fmoc-Linker-BHA resin (360 mg, 0.2 mmol) from Example 29 were subjected to solid phase synthesis using protocol 1 described above. All couplings were performed using HBTU in DMF as the coupling agent and DIPEA (3 equiv.) as base. Five coupling cycles were performed of one cycle each with Fmoc-Gly (180 mg, 0.6 mmol) and HBTU (226 mg, 0.6 mmol), Fmoc-Trp (260 mg, 0.6 mmol) and HBTU (226 mg, 0.6 mmol), Fmoc-Arg (Pmc) (400 mg, 0.6 mmol) and HBTU (226 mg, 0.6 mmol), Fmoc-(D)Phe (240 mg, 0.6 mmol) and HBTU (226 mg, 0.6 mmol), **Fmoc-5-MeO(D,L)Atc** (300 mg 0.6 mmol) and HBTU (226 mg, 0.6 mmol). The peptide resin was carried through steps 1 - 5 of protocol 1, washed with CH_2Cl_2 (three times) and treated with 1 mL valeric anhydride in 6% DIPEA/CH_2Cl_2 for 30 minutes. The resin was filtered and washed successively with 20 ml each of CH_2Cl_2 (two times), isopropanol, and CH_2Cl_2 (three times). The resin was dried under vacuum to yield 610 mg of Pentyl-Pentapeptide resin.

The Pentyl-Pentapeptide resin was treated with 40 µL ethanedithiol, 40 µL dimethylsulfide, 120 µL anisole, and 4 mL trifluoroacetic acid at room temperature for 180 min. The resin was filtered off, washed with ~2 ml TFA and the filtrates precipitated in chilled ethyl ether. The precipitates were centrifuged and the ether layer decanted. The residue was washed with two or three volumes of Et_2O and recentrifuged and the crude product was dried under vacuum to yield 155 mg of an off-white solid.

This crude material was purified by preparative HPLC on a Vydac C18-column (2.5 x 20 cm) and eluted with a linear gradient of 10-60% B (buffer A: 0.1% TFA/H_2O, buffer B: 0.1% TFA/CH_3CN) in 60 min., flow rate 8ml/min, detection 280 nm. The main peak was cut by analytical HPLC analysis of collected fractions, pooled and lyophilized to yield 46 mg (27 %) of a white, amorphous powder. This compound was homogeneous by HPLC. LR-Electrospray: $C_{45}H_{58}N_{10}O_7$, cal 851 observed: m/z (852 M+H).

EXAMPLE 87

Penta-5-EtO-(D,L)Atc-(D)Phe-Arg-Trp-Gly -NH_2



Fmoc-Linker-BHA resin (360 mg, 0.2 mmol) from Example 29 were subjected to solid phase synthesis using protocol 1 described above. All couplings were performed using HBTU in DMF as the coupling agent and DIPEA (3 equiv.) as base. Five coupling cycles were performed of one cycle each with Fmoc-Gly (180 mg, 0.6 mmol) and HBTU (226 mg, 0.6 mmol), Fmoc-Trp (260 mg, 0.6 mmol) and HBTU (226 mg, 0.6 mmol), Fmoc-Arg (Pmc)

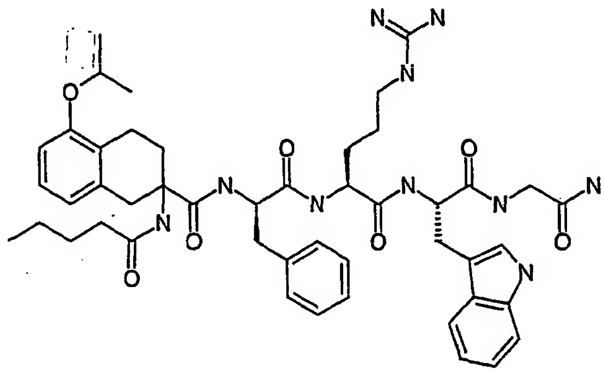
(400 mg, 0.6 mmol) and HBTU (226 mg, 0.6 mmol), Fmoc-(D)Phe (240 mg, 0.6 mmol) and HBTU (226 mg, 0.6 mmol), **Fmoc-5-EtO(D,L)Atc** (310 mg 0.6 mmol) and HBTU (226 mg, 0.6 mmol). The peptide resin was carried through steps 1 - 5 of protocol 1, washed with CH_2Cl_2 (three times) and treated with 1 mL valeric anhydride in 6% DIPEA/CH_2Cl_2 for 30 minutes. The resin was filtered and washed successively with 20 ml each of CH_2Cl_2 (two times), isopropanol, and CH_2Cl_2 (three times). The resin was dried under vacuum to yield 594 mg of Pentyl-Pentapeptide resin.

The Pentyl-Pentapeptide resin was treated with 40 μL ethanedithiol, 40 μL dimethylsulfide, 120 μL anisole, and 4 mL trifluoroacetic acid at room temperature for 180 min. The resin was filtered off, washed with ~2 ml TFA and the filtrates precipitated in chilled ethyl ether. The precipitates were centrifuged and the ether layer decanted. The residue was washed with two or three volumes of Et_2O and recentrifuged and the crude product was dried under vacuum to yield 145 mg of an off-white solid.

This crude material was purified by preparative HPLC on a Vydac C18-column (2.5 x 20 cm) and eluted with a linear gradient of 10-60% B (buffer A: 0.1% TFA/H_2O, buffer B: 0.1% TFA/CH_3CN) in 60 min., flow rate 8ml/min, detection 280 nm. The main peak was cut by analytical HPLC analysis of collected fractions, pooled and lyophilized to yield 41 mg (24 %) of a white, amorphous powder. This compound was homogeneous by HPLC. LR-Electrospray: $C_{46}H_{60}N_{10}O_7$, cal 865 observed: m/z (866 M+H).

EXAMPLE 88

Penta-5-**iPrO-(D,L)Atc**-(D)Phe-Arg-Trp-Gly-NH_2



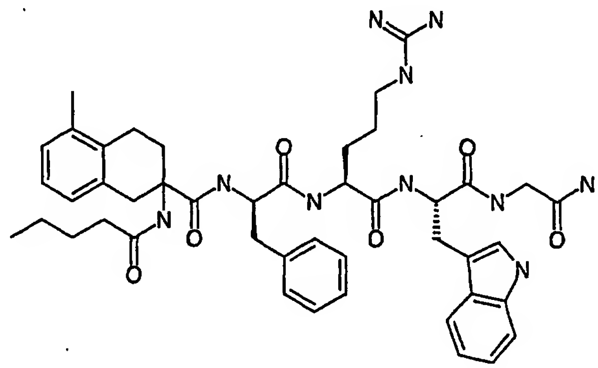
Fmoc-Linker-BHA resin (360 mg, 0.2 mmol) from Example 29 were subjected to solid phase *synthesis using protocol 1 described above. All couplings were performed using HBTU in* DMF as the coupling agent and DIPEA (3 equiv.) as base. Five coupling cycles were performed of one cycle each with Fmoc-Gly (180 mg, 0.6 mmol) and HBTU (226 mg, 0.6 mmol), Fmoc-Trp (260 mg, 0.6 mmol) and HBTU (226 mg, 0.6 mmol), Fmoc-Arg (Pmc) (400 mg, 0.6 mmol) and HBTU (226 mg, 0.6 mmol), Fmoc-(D)Phe (240 mg, 0.6 mmol) and HBTU (226 mg, 0.6 mmol), **Fmoc-5-iPrO(D,L)Atc** (310 mg 0.6 mmol) and HBTU (226 mg, 0.6 mmol). The peptide resin was carried through steps 1 - 5 of protocol 1, washed with CH_2Cl_2 (three times) and treated with 1 mL valeric anhydride in 6% DIPEA/CH_2Cl_2 for 30 minutes. The resin was filtered and washed successively with 20 ml each of CH_2Cl_2 (two times), isopropanol, and CH_2Cl_2 (three times). The resin was dried under vacuum to yield 580 mg of Pentyl-Pentapeptide resin.

The Pentyl-Pentapeptide resin was treated with 40 μL ethanedithiol, 40 μL dimethylsulfide, 120 μL anisole, and 4 mL trifluoroacetic acid at room temperature for 180 min. The resin was filtered off, washed with ~2 ml TFA and the filtrates precipitated in chilled ethyl ether. The precipitates were centrifuged and the ether layer decanted. The residue was washed with two or three volumes of Et_2O and recentrifuged and the crude product was dried under vacuum to yield 142 mg of an off-white solid.

This crude material was purified by preparative HPLC on a Vydac C18-column (2.5 x 20 cm) and eluted with a linear gradient of 10-60% B (buffer A: 0.1% TFA/H_2O, buffer B: 0.1% TFA/CH_3CN) in 60 min., flow rate 8ml/min, detection 280 nm. The main peak was cut by analytical HPLC analysis of collected fractions, pooled and lyophilized to yield 43 mg (25 %) of a white, amorphous powder. This compound was homogeneous by HPLC. LR-Electrospray: $C_{47}H_{62}N_{10}O_7$, cal 879 observed: m/z (880 M+H).

EXAMPLE 89

Penta-**5-Me-(D,L)Atc**-(D)Phe-Arg-Trp-Gly -NH_2



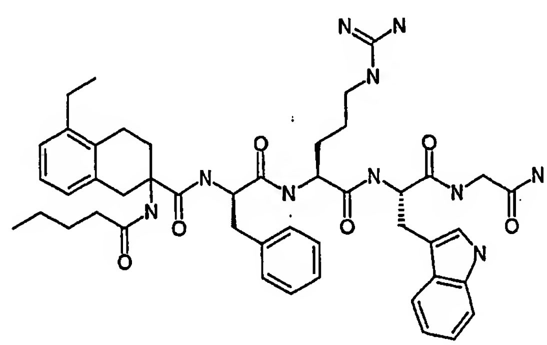
Fmoc-Linker-BHA resin (360 mg, 0.2 mmol) from Example 29 were subjected to solid phase synthesis using protocol 1 described above. All couplings were performed using HBTU in DMF as the coupling agent and DIPEA (3 equiv.) as base. Five coupling cycles were performed of one cycle each with Fmoc-Gly (180 mg, 0.6 mmol) and HBTU (226 mg, 0.6 mmol), Fmoc-Trp (260 mg, 0.6 mmol) and HBTU (226 mg, 0.6 mmol), Fmoc-Arg (Pmc) (400 mg, 0.6 mmol) and HBTU (226 mg, 0.6 mmol), Fmoc-(D)Phe (240 mg, 0.6 mmol) and HBTU (226 mg, 0.6 mmol), **Fmoc-5-Me(D,L)Atc** (290 mg, 0.6 mmol) and HBTU (226 mg, 0.6 mmol).The peptide resin was carried through steps 1 - 5 of protocol 1, washed with CH_2Cl_2 (three times) and treated with 1 mL valeric anhydride in 6% DIPEA/CH_2Cl_2 for 30 minutes. The resin was filtered and washed successively with 20 ml each of CH_2Cl_2 (two times), isopropanol, and CH_2Cl_2 (three times). The resin was dried under vacuum to yield 610 mg of Pentyl-Pentapeptide resin.

The Pentyl-Pentapeptide resin was treated with 40 µL ethanedithiol, 40 µL dimethylsulfide, 120 µL anisole, and 4 mL trifluoroacetic acid at room temperature for 180 min. The resin was filtered off, washed with ~2 ml TFA and the filtrates precipitated in chilled ethyl ether. The precipitates were centrifuged and the ether layer decanted. The residue was washed with two or three volumes of Et_2O and recentrifuged and the crude product was dried under vacuum to yield 143 of an off-white solid.

This crude material was purified by preparative HPLC on a Vydac C18-column (2.5 x 20 cm) and eluted with a linear gradient of 10-60% B (buffer A: 0.1% TFA/H_2O, buffer B: 0.1% TFA/CH_3CN) in 60 min., flow rate 8ml/min, detection 280 nm. The main peak was cut by analytical HPLC analysis of collected fractions, pooled and lyophilized to yield 40 mg (24 %) of a white, amorphous powder. This compound was homogeneous by HPLC. LR-Electrospray: $C_{45}H_{58}N_{10}O_6$, cal 835 observed: m/z (836 M+H).

EXAMPLE 90

Penta-5-Et-(D,L)Atc-(D)Phe-Arg-Trp-Gly -NH_2



Fmoc-Linker-BHA resin (360 mg, 0.2 mmol) from Example 29 were subjected to solid phase synthesis using protocol 1 described above. All couplings were performed using HBTU in DMF as the coupling agent and DIPEA (3 equiv.) as base. Five coupling cycles were performed of one cycle each with Fmoc-Gly (180 mg, 0.6 mmol) and HBTU (226 mg, 0.6 mmol), Fmoc-Trp (260 mg, 0.6 mmol) and HBTU (226 mg, 0.6 mmol), Fmoc-Arg (Pmc) (400 mg, 0.6 mmol) and HBTU (226 mg, 0.6 mmol), Fmoc-(D)Phe (240 mg, 0.6 mmol) and

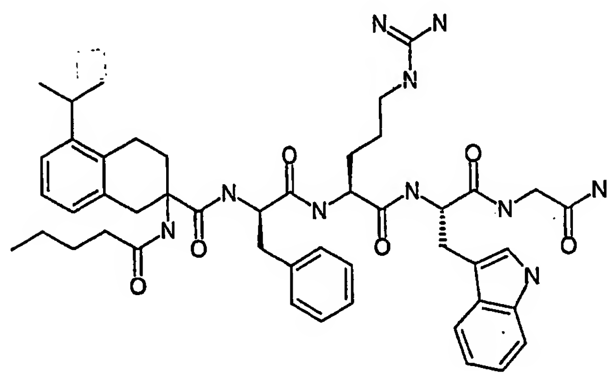
HBTU (226 mg, 0.6 mmol), **Fmoc-5-Et(D,L)Atc** (285 mg, 0.6 mmol) and HBTU (226 mg, 0.6 mmol). The peptide resin was carried through steps 1 - 5 of protocol 1, washed with CH_2Cl_2 (three times) and treated with 1 mL valeric anhydride in 6% DIPEA/CH_2Cl_2 for 30 minutes. The resin was filtered and washed successively with 20 ml each of CH_2Cl_2 (two times), isopropanol, and CH_2Cl_2 (three times). The resin was dried under vacuum to yield 620 mg of Pentyl-Pentapeptide resin

The Pentyl-Pentapeptide resin was treated with 40 µL ethanedithiol, 40 µL dimethylsulfide, 120 µL anisole, and 4 mL trifluoroacetic acid at room temperature for 180 min. The resin was filtered off, washed with ~2 ml TFA and the filtrates precipitated in chilled ethyl ether. The precipitates were centrifuged and the ether layer decanted. The residue was washed with two or three volumes of Et_2O and recentrifuged and the crude product was dried under vacuum to yield 154 mg of an off-white solid.

This crude material was purified by preparative HPLC on a Vydac C18-column (2.5 x 20 cm) and eluted with a linear gradient of 10-60% B (buffer A: 0.1% TFA/H_2O, buffer B: 0.1% TFA/CH_3CN) in 60 min., flow rate 8ml/min, detection 280 nm. The main peak was cut by analytical HPLC analysis of collected fractions, pooled and lyophilized to yield 53 mg (31 %) of a white, amorphous powder. This compound was homogeneous by HPLC. LR-Electrospray: $C_{46}H_{60}N_{10}O_6$, cal 849 observed: m/z (850 M+H).

EXAMPLE 91

Penta-5-iPr-(D,L)Atc-(D)Phe-Arg-Trp-Gly-NH_2



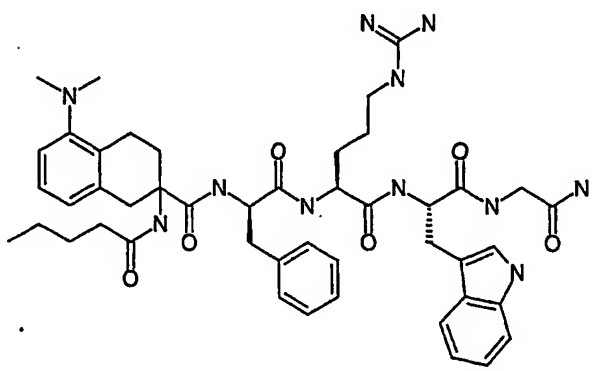
Fmoc-Linker-BHA resin (360 mg, 0.2 mmol) from Example 29 were subjected to solid phase synthesis using protocol 1 described above. All couplings were performed using HBTU in DMF as the coupling agent and DIPEA (3 equiv.) as base. Five coupling cycles were performed of one cycle each with Fmoc-Gly (180 mg, 0.6 mmol) and HBTU (226 mg, 0.6 mmol), Fmoc-Trp (260 mg, 0.6 mmol) and HBTU (226 mg, 0.6 mmol), Fmoc-Arg (Pmc) (400 mg, 0.6 mmol) and HBTU (226 mg, 0.6 mmol), Fmoc-(D)Phe (240 mg, 0.6 mmol) and HBTU (226 mg, 0.6 mmol), **Fmoc-5-iPr(D,L)Atc** (300 mg, 0.6 mmol) and HBTU (226 mg, 0.6 mmol). The peptide resin was carried through steps 1 - 5 of protocol 1, washed with CH_2Cl_2 (three times) and treated with 1 mL valeric anhydride in 6% DIPEA/CH_2Cl_2 for 30 minutes. The resin was filtered and washed successively with 20 ml each of CH_2Cl_2 (two times), isopropanol, and CH_2Cl_2 (three times). The resin was dried under vacuum to yield 600 mg of Pentyl-Pentapeptide resin.

The Pentyl-Pentapeptide resin was treated with 40 μL ethanedithiol, 40 μL dimethylsulfide, 120 μL anisole, and 4 mL trifluoroacetic acid at room temperature for 180 min. The resin was filtered off, washed with ~2 ml TFA and the filtrates precipitated in chilled ethyl ether. The precipitates were centrifuged and the ether layer decanted. The residue was washed with two or three volumes of Et_2O and recentrifuged and the crude product was dried under vacuum to yield 149 mg of an off-white solid.

This crude material was purified by preparative HPLC on a Vydac C18-column (2.5 x 20 cm) and eluted with a linear gradient of 10-60% B (buffer A: 0.1% TFA/H_2O, buffer B: 0.1% TFA/CH_3CN) in 60 min., flow rate 8ml/min, detection 280 nm. The main peak was cut by analytical HPLC analysis of collected fractions, pooled and lyophilized to yield 47 mg (27%) of a white, amorphous powder. This compound was homogeneous by HPLC. LR-Electrospray: $C_{47}H_{62}N_{10}O_6$, cal 863 observed: m/z (864 M+H).

EXAMPLE 92

Penta-**5-DmaAtc**-(D)Phe-Arg-Trp-Gly-NH_2 (peak 1)



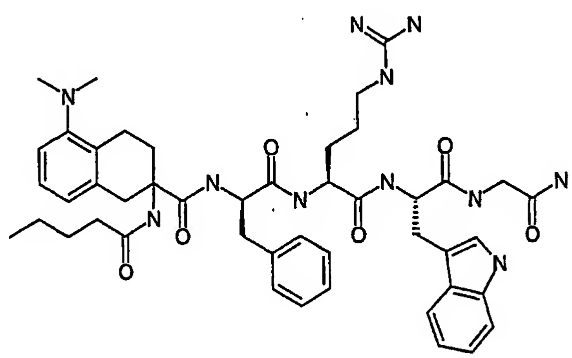
Fmoc-Linker-BHA resin (360 mg, 0.2 mmol) from Example 29 were subjected to solid phase synthesis using protocol 1 described above. All couplings were performed using HBTU in DMF as the coupling agent and DIPEA (3 equiv.) as base. Five coupling cycles were performed of one cycle each with Fmoc-Gly (180 mg, 0.6 mmol) and HBTU (226 mg, 0.6 mmol), Fmoc-Trp (260 mg, 0.6 mmol) and HBTU (226 mg, 0.6 mmol), Fmoc-Arg (Pmc) (400 mg, 0.6 mmol) and HBTU (226 mg, 0.6 mmol), Fmoc-(D)Phe (240 mg, 0.6 mmol) and HBTU (226 mg, 0.6 mmol), **Fmoc-5-Dma(D,L)Atc** (300 mg, 0.6 mmol) and HBTU (226 mg, 0.6 mmol). The peptide resin was carried through steps 1 - 5 of protocol 1, washed with CH_2Cl_2 (three times) and treated with 1 mL valeric anhydride in 6% DIPEA/CH_2Cl_2 for 30 minutes. The resin was filtered and washed successively with 20 ml each of CH_2Cl_2 (two times), isopropanol, and CH_2Cl_2 (three times). The resin was dried under vacuum to yield 610 mg of Pentyl-Pentapeptide resin.

The Pentyl-Pentapeptide resin was treated with 40 μL ethanedithiol, 40 μL dimethylsulfide, 120 μL anisole, and 4 mL trifluoroacetic acid at room temperature for 180 min. The resin was filtered off, washed with ~2 ml TFA and the filtrates precipitated in chilled ethyl ether. The precipitates were centrifuged and the ether layer decanted. The residue was washed with two or three volumes of Et_2O and recentrifuged and the crude product was dried under vacuum to yield 149 of an off-white solid.

This crude material was purified by preparative HPLC on a Vydac C18-column (2.5 x 20 cm) and eluted with a linear gradient of 10-60% B (buffer A: 0.1% TFA/H_2O, buffer B: 0.1% TFA/CH_3CN) in 60 min., flow rate 8ml/min, detection 280 nm. The first main peak was cut by analytical HPLC analysis of collected fractions, pooled and lyophilized to yield 22 mg (13 %) of a white, amorphous powder. This compound was homogeneous by HPLC. LR-Electrospray: $C_{46}H_{61}N_{11}O_6$, cal 864 observed: m/z (865 M+H).

EXAMPLE 93

Penta-**5-DmaAtc**-(D)Phe-Arg-Trp-Gly-NH_2 (peak 2)



Fmoc-Linker-BHA resin (360 mg, 0.2 mmol) from Example 29 were subjected to solid phase synthesis using protocol 1 described above. All couplings were performed using HBTU in DMF as the coupling agent and DIPEA (3 equiv.) as base. Five coupling cycles were performed of one cycle each with Fmoc-Gly (180 mg, 0.6 mmol) and HBTU (226 mg, 0.6 mmol), Fmoc-Trp (260 mg, 0.6 mmol) and HBTU (226 mg, 0.6 mmol), Fmoc-Arg (Pmc) (400 mg, 0.6 mmol) and HBTU (226 mg, 0.6 mmol), Fmoc-(D)Phe (240 mg, 0.6 mmol) and

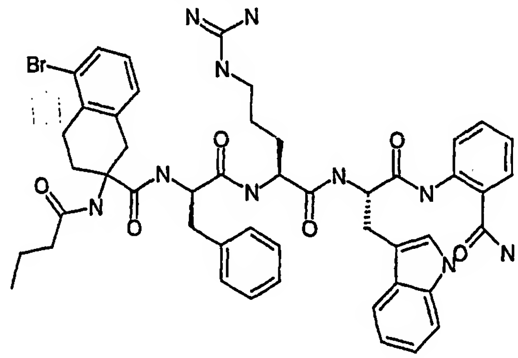
HBTU (226 mg, 0.6 mmol), **Fmoc-5-Dma(D,L)Atc** (300 mg, 0.6 mmol) and HBTU (226 mg, 0.6 mmol). The peptide resin was carried through steps 1 - 5 of protocol 1, washed with CH_2Cl_2 (three times) and treated with 1 mL valeric anhydride in 6% DIPEA/CH_2Cl_2 for 30 minutes. The resin was filtered and washed successively with 20 ml each of CH_2Cl_2 (two times), isopropanol, and CH_2Cl_2 (three times). The resin was dried under vacuum to yield 610 mg of Pentyl-Pentapeptide resin.

The Pentyl-Pentapeptide resin was treated with 40 µL ethanedithiol, 40 µL dimethylsulfide, 120 µL anisole, and 4 mL trifluoroacetic acid at room temperature for 180 min. The resin was filtered off, washed with ~2 ml TFA and the filtrates precipitated in chilled ethyl ether. The precipitates were centrifuged and the ether layer decanted. The residue was washed with two or three volumes of Et_2O and recentrifuged and the crude product was dried under vacuum to yield 149 of an off-white solid.

This crude material was purified by preparative HPLC on a Vydac C18-column (2.5 x 20 cm) and eluted with a linear gradient of 10-60% B (buffer A: 0.1% TFA/H_2O, buffer B: 0.1% TFA/CH_3CN) in 60 min., flow rate 8ml/min, detection 280 nm. The **second** main peak was cut by analytical HPLC analysis of collected fractions, pooled and lyophilized to yield 27 mg (16 %) of a white, amorphous powder. This compound was homogeneous by HPLC. LR-Electrospray: $C_{46}H_{61}N_{11}O_6$, cal 864 observed: m/z (865 M+H).

EXAMPLE 94

Bu-(D,L)5-BrAtc-(D)Phe-Arg-Trp-2-Aba-NH_2



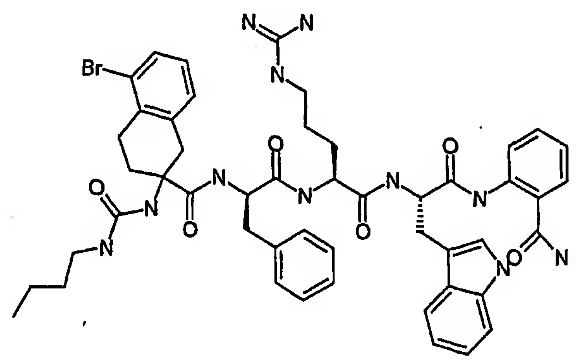
Fmoc-Linker-BHA resin (360 mg, 0.2 mmol) from Example 29 were subjected to solid phase synthesis using protocol 1 described above. All couplings were performed using HBTU in DMF as the coupling agent and DIPEA (3 equiv.) as base. Five coupling cycles were performed of one cycle each with **Fmoc-2-Aba** (215 mg, 0.6 mmol) and HBTU (226 mg, 0.6 mmol), Fmoc-Trp (260 mg, 0.6 mmol) and HBTU (226 mg, 0.6 mmol), Fmoc-Arg (Pmc) (400 mg, 0.6 mmol) and HBTU (226 mg, 0.6 mmol), Fmoc-(D)Phe (240 mg, 0.6 mmol) and HBTU (226 mg, 0.6 mmol), **Fmoc-(D,L) 5-BrAtc** (310 mg 0.6 mmol) and HBTU (226 mg, 0.6 mmol). The peptide resin was carried through steps 1 - 5 of protocol 1, washed with CH_2Cl_2 (three times) and treated with 1 ml of butyric anhydride in 6% DIPEA/CH_2Cl_2 for 30 minutes. The resin was filtered and washed successively with 20 ml each of CH_2Cl_2 (two times), isopropanol, and CH_2Cl_2 (three times). The resin was dried under vacuum to yield 600 mg of butyl Pentapeptide resin.

The butyl Pentapeptide resin was treated with 40 µL ethanedithiol, 40 µL dimethylsulfide, 120 µL anisole, and 4 mL trifluoroacetic acid at room temperature for 180 min. The resin was filtered off, washed with ~2 ml TFA and the filtrates precipitated in chilled ethyl ether. The precipitates were centrifuged and the ether layer decanted. The residue was washed with two or three volumes of Et_2O and recentrifuged and the crude product was dried under vacuum to yield 141 mg of an off-white solid.

This crude material was purified by preparative HPLC on a Vydac C18-column (2.5 x 20 cm) and eluted with a linear gradient of 10-60% B (buffer A: 0.1% TFA/H_2O, buffer B: 0.1% TFA/CH_3CN) in 60 min., flow rate 8ml/min, detection 280 nm. The main peak was cut by analytical HPLC analysis of collected fractions, pooled and lyophilized to yield 35 mg (19 %) of a white, amorphous powder. This compound was homogeneous by HPLC. LR-Electrospray: $C_{48}H_{55}N_{10}O_6Br$, cal: 948 observed: m/z (949 M+H).

EXAMPLE 95

Bu-carbamoyl-(D,L)-5-BrAtc-(D)Phe-Arg-Trp-2-Aba-NH_2



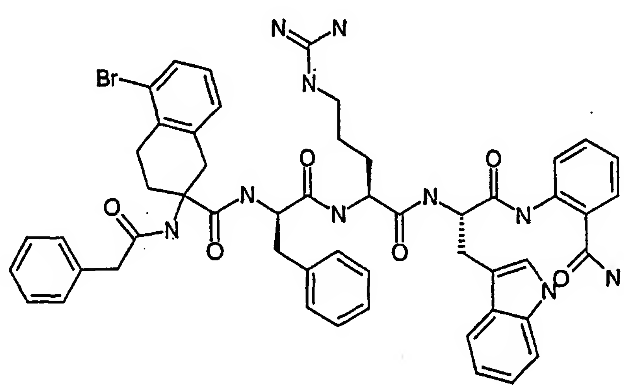
Fmoc-Linker-BHA resin (360 mg, 0.2 mmol) from Example 29 were subjected to solid phase synthesis using protocol 1 described above. All couplings were performed using HBTU in DMF as the coupling agent and DIPEA (3 equiv.) as base. Five coupling cycles were performed of one cycle each with **Fmoc-2-Aba** (215 mg, 0.6 mmol) and HBTU (226 mg, 0.6 mmol), Fmoc-Trp (260 mg, 0.6 mmol) and HBTU (226 mg, 0.6 mmol), Fmoc-Arg (Pmc) (400 mg, 0.6 mmol) and HBTU (226 mg, 0.6 mmol), Fmoc-(D)Phe (240 mg, 0.6 mmol) and HBTU (226 mg, 0.6 mmol), **Fmoc-(D,L)-5-BrAtc** (310 mg 0.6 mmol) and HBTU (226 mg, 0.6 mmol). The peptide resin was carried through steps 1 - 5 of protocol 1, washed with CH_2Cl_2 (three times) and treated with n-butyl isocyanate (5 eq) in 6% DIPEA/CH_2Cl_2 for 12 hours . The resin was filtered and washed successively with 20 ml each of CH_2Cl_2 (two times), isopropanol, and CH_2Cl_2 (three times). The resin was dried under vacuum to yield 620 mg of butyl carbamoyl-Pentapeptide resin.

The butyl-carbamoyl Pentapeptide resin was treated with 40 μL ethanedithiol, 40 μL dimethylsulfide, 120 μL anisole, and 4 mL trifluoroacetic acid at room temperature for 180 min. The resin was filtered off, washed with ~2 ml TFA and the filtrates precipitated in chilled ethyl ether. The precipitates were centrifuged and the ether layer decanted. The residue was washed with two or three volumes of Et_2O and recentrifuged and the crude product was dried under vacuum to yield 153 mg of an off-white solid.

This crude material was purified by preparative HPLC on a Vydac C18-column (2.5 x 20 cm) and eluted with a linear gradient of 10-60% B (buffer A: 0.1% TFA/H_2O, buffer B: 0.1% TFA/CH_3CN) in 60 min., flow rate 8ml/min, detection 280 nm. The main peak was cut by analytical HPLC analysis of collected fractions, pooled and lyophilized to yield 41 mg (21 %) of a white, amorphous powder. This compound was homogeneous by HPLC. LR-Electrospray: $C_{49}H_{58}N_{11}O_6Br$, cal: 977 observed: m/z (978 M+H).

EXAMPLE 96

Phenylacetyl-(D,L)-5-BrAtc-(D)Phe-Arg-Trp-2-Aba-NH_2



Fmoc-Linker-BHA resin (360 mg, 0.2 mmol) from Example 29 were subjected to solid phase synthesis using protocol 1 described above. All couplings were performed using HBTU in DMF as the coupling agent and DIPEA (3 equiv.) as base. Five coupling cycles were performed of one cycle each with **Fmoc-2-Aba** (215 mg, 0.6 mmol) and HBTU (226 mg, 0.6 mmol), Fmoc-Trp (260 mg, 0.6 mmol) and HBTU (226 mg, 0.6 mmol), Fmoc-Arg (Pmc)

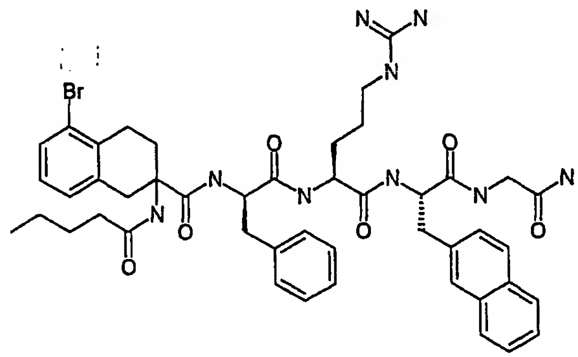
(400 mg, 0.6 mmol) and HBTU (226 mg, 0.6 mmol), Fmoc-(D)Phe (240 mg, 0.6 mmol) and HBTU (226 mg, 0.6 mmol), **Fmoc-(D,L)-5-BrAtc** (310 mg 0.6 mmol) and HBTU (226 mg, 0.6 mmol). The peptide resin was carried through steps 1 - 5 of protocol 1, washed with CH_2Cl_2 (three times) and treated with phenylacetic acid, HBTU in DMF. The resin was filtered and washed successively with 20 ml each of CH_2Cl_2 (two times), isopropanol, and CH_2Cl_2 (three times). The resin was dried under vacuum to yield 610 mg of Phenylacetyl Pentapeptide resin.

The phenylacetyl Pentapeptide resin was treated with 40 μL ethanedithiol, 40 μL dimethylsulfide, 120 μL anisole, and 4 mL trifluoroacetic acid at room temperature for 180 min. The resin was filtered off, washed with ~2 ml TFA and the filtrates precipitated in chilled ethyl ether. The precipitates were centrifuged and the ether layer decanted. The residue was washed with two or three volumes of Et_2O and recentrifuged and the crude product was dried under vacuum to yield 148 mg of an off-white solid.

This crude material was purified by preparative HPLC on a Vydac C18-column (2.5 x 20 cm) and eluted with a linear gradient of 10-60% B (buffer A: 0.1% TFA/H_2O, buffer B: 0.1% TFA/CH_3CN) in 60 min., flow rate 8ml/min, detection 280 nm. The main peak was cut by analytical HPLC analysis of collected fractions, pooled and lyophilized to yield 38 mg (19 %) of a white, amorphous powder. This compound was homogeneous by HPLC. LR-Electrospray: $C_{52}H_{55}N_{10}O_6Br$, cal: 996 observed: m/z (997 M+H).

EXAMPLE 97

Penta-(D,L)-5-BrAtc-(D)Phe-Arg-(2)Nal-Gly-NH_2



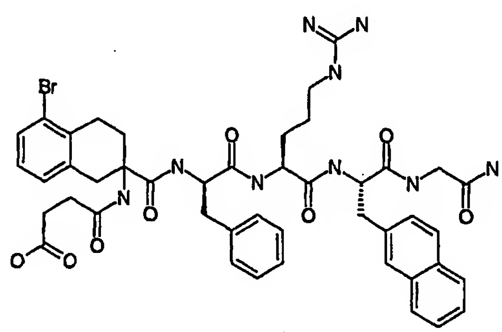
Fmoc-Linker-BHA resin (360 mg, 0.2 mmol) from Example 29 were subjected to solid phase synthesis using protocol 1 described above. All couplings were performed using HBTU in DMF as the coupling agent and DIPEA (3 equiv.) as base. Five coupling cycles were performed of one cycle each with Fmoc-Gly (180 mg, 0.6 mmol) and HBTU (226 mg, 0.6 mmol), **Fmoc-(2)Nal** (265 mg, 0.6 mmol) and HBTU (226 mg, 0.6 mmol), Fmoc-Arg (Pmc) (400 mg, 0.6 mmol) and HBTU (226 mg, 0.6 mmol), Fmoc-(D)Phe (240 mg, 0.6 mmol) and HBTU (226 mg, 0.6 mmol), **Fmoc-(D,L)-5-BrAtc** (310 mg 0.6 mmol) and HBTU (226 mg, 0.6 mmol). The peptide resin was carried through steps 1 - 5 of protocol 1, washed with CH_2Cl_2 (three times) and treated with 1 mL valeric anhydride in 6% DIPEA/CH_2Cl_2 for 30 minutes. The resin was filtered and washed successively with 20 ml each of CH_2Cl_2 (two times), isopropanol, and CH_2Cl_2 (three times). The resin was dried under vacuum to yield 620mg of Pentyl-Pentapeptide resin.

The Pentyl-Pentapeptide resin was treated with 40 μL ethanedithiol, 40 μL dimethylsulfide, 120 μL anisole, and 4 mL trifluoroacetic acid at room temperature for 180 min. The resin was filtered off, washed with ~2 ml TFA and the filtrates precipitated in chilled ethyl ether. The precipitates were centrifuged and the ether layer decanted. The residue was washed with two or three volumes of Et_2O and recentrifuged and the crude product was dried under vacuum to yield 162 mg of an off-white solid.

This crude material was purified by preparative HPLC on a Vydac C18-column (2.5 x 20 cm) and eluted with a linear gradient of 10-60% B (buffer A: 0.1% TFA/H_2O, buffer B: 0.1% TFA/CH_3CN) in 60 min., flow rate 8ml/min, detection 280 nm. The main peak was cut by analytical HPLC analysis of collected fractions, pooled and lyophilized to yield 60 mg (33 %) of a white, amorphous powder. This compound was homogeneous by HPLC. LR-Electrospray: $C_{46}H_{56}N_9O_6Br$, cal: 911 observed: m/z (912 M+H).

EXAMPLE 98

3-carboxylpropanoyl-(D,L)-5-BrAtc-(D)Phe-Arg-(2)Nal-Gly-NH_2



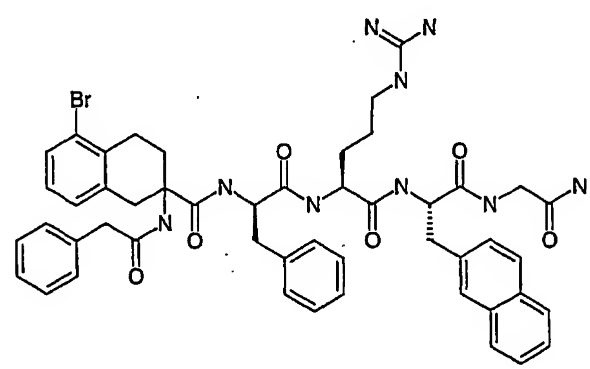
Fmoc-Linker-BHA resin (360 mg, 0.2 mmol) from Example 29 were subjected to solid phase synthesis using protocol 1 described above. All couplings were performed using HBTU in DMF as the coupling agent and DIPEA (3 equiv.) as base. Five coupling cycles were performed of one cycle each with Fmoc-Gly (180 mg, 0.6 mmol) and HBTU (226 mg, 0.6 mmol), **Fmoc-(2)Nal** (265 mg, 0.6 mmol) and HBTU (226 mg, 0.6 mmol), Fmoc-Arg (Pmc) (400 mg, 0.6 mmol) and HBTU (226 mg, 0.6 mmol), Fmoc-(D)Phe (240 mg, 0.6 mmol) and HBTU (226 mg, 0.6 mmol), **Fmoc-(D,L)-5-BrAtc** (310 mg 0.6 mmol) and HBTU (226 mg, 0.6 mmol). The peptide resin was carried through steps 1 - 5 of protocol 1, washed with CH_2Cl_2 (three times) and treated with succinic acid, HBTU in DMF. The resin was filtered and washed successively with 20 ml each of CH_2Cl_2 (two times), isopropanol, and CH_2Cl_2 (three times). The resin was dried under vacuum to yield 610 mg of 3-carboxylpropanoyl-Pentapeptide resin.

The 3-carboxylpropanoyl Pentapeptide resin was treated with 40 μL ethanedithiol, 40 μL dimethylsulfide, 120 μL anisole, and 4 mL trifluoroacetic acid at room temperature for 180 min. The resin was filtered off, washed with ~2 ml TFA and the filtrates precipitated in chilled ethyl ether. The precipitates were centrifuged and the ether layer decanted. The residue was washed with two or three volumes of Et_2O and recentrifuged and the crude product was dried under vacuum to yield 158 mg of an off-white solid.

This crude material was purified by preparative HPLC on a Vydac C18-column (2.5 x 20 cm) and eluted with a linear gradient of 10-60% B (buffer A: 0.1% TFA/H_2O, buffer B: 0.1% TFA/CH_3CN) in 60 min., flow rate 8ml/min, detection 280 nm. The main peak was cut by analytical HPLC analysis of collected fractions, pooled and lyophilized to yield 55 mg (30 %) of a white, amorphous powder. This compound was homogeneous by HPLC. LR-Electrospray: $C_{45}H_{52}N_9O_8Br$, cal: 927 observed: m/z (928 M+H).

EXAMPLE 99

Phenylacetyl-(D,L)-5-BrAtc-(D)Phe-Arg-(2)Nal-Gly-NH_2



Fmoc-Linker-BHA resin (360 mg, 0.2 mmol) from Example 29 were subjected to solid phase synthesis using protocol 1 described above. All couplings were performed using HBTU in DMF as the coupling agent and DIPEA (3 equiv.) as base. Five coupling cycles were performed of one cycle each with Fmoc-Gly (180 mg, 0.6 mmol) and HBTU (226 mg, 0.6 mmol), **Fmoc-(2)Nal** (265 mg, 0.6 mmol) and HBTU (226 mg, 0.6 mmol), Fmoc-Arg (Pmc)

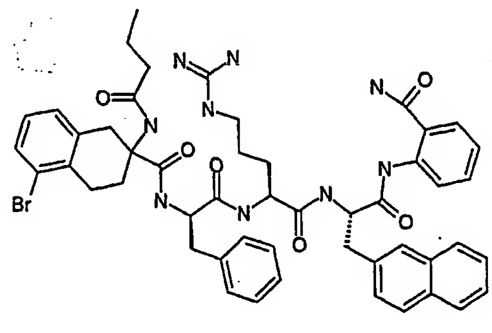
(400 mg, 0.6 mmol) and HBTU (226 mg, 0.6 mmol), Fmoc-(D)Phe (240 mg, 0.6 mmol) and HBTU (226 mg, 0.6 mmol), **Fmoc-(D,L)-5-BrAtc** (310 mg 0.6 mmol) and HBTU (226 mg, 0.6 mmol). The peptide resin was carried through steps 1 - 5 of protocol 1, washed with CH_2Cl_2 (three times) and treated with phenyl acetic acid, HBTU in DMF. The resin was filtered and washed successively with 20 ml each of CH_2Cl_2 (two times), isopropanol, and CH_2Cl_2 (three times). The resin was dried under vacuum to yield 600 mg of phenylacetyl Pentapeptide resin.

The phenylacetyl Pentapeptide resin was treated with 40 μL ethanedithiol, 40 μL dimethylsulfide, 120 μL anisole, and 4 mL trifluoroacetic acid at room temperature for 180 min. The resin was filtered off, washed with ~2 ml TFA and the filtrates precipitated in chilled ethyl ether. The precipitates were centrifuged and the ether layer decanted. The residue was washed with two or three volumes of Et_2O and recentrifuged and the crude product was dried under vacuum to yield 161 mg of an off-white solid.

This crude material was purified by preparative HPLC on a Vydac C18-column (2.5 x 20 cm) and eluted with a linear gradient of 10-60% B (buffer A: 0.1% TFA/H_2O, buffer B: 0.1% TFA/CH_3CN) in 60 min., flow rate 8ml/min, detection 280 nm. The main peak was cut by analytical HPLC analysis of collected fractions, pooled and lyophilized to yield 58 mg (30 %) of a white, amorphous powder. This compound was homogeneous by HPLC. LR-Electrospray: $C_{49}H_{54}N_9O_6Br$., cal: 945 observed: m/z (946 M+H).

EXAMPLE 100

Bu-(D,L)-5-BrAtc-(D)Phe-Arg-(2)Nal-2-Aba-NH_2



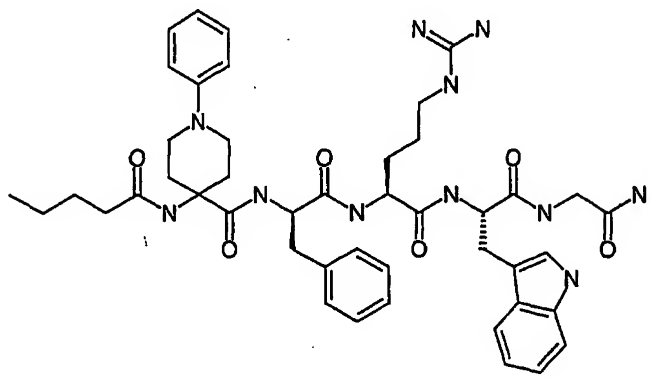
Fmoc-Linker-BHA resin (360 mg, 0.2 mmol) from Example 29 were subjected to solid phase synthesis using protocol 1 described above. All couplings were performed using HBTU in DMF as the coupling agent and DIPEA (3 equiv.) as base. Five coupling cycles were performed of one cycle each with **Fmoc-2-Aba** (215 mg, 0.6 mmol) and HBTU (226 mg, 0.6 mmol), **Fmoc-(2)Nal** (265 mg, 0.6 mmol) and HBTU (226 mg, 0.6 mmol), Fmoc-Arg (Pmc) (400 mg, 0.6 mmol) and HBTU (226 mg, 0.6 mmol), Fmoc-(D)Phe (240 mg, 0.6 mmol) and HBTU (226 mg, 0.6 mmol), **Fmoc-(D,L)-5-BrAtc** (310 mg 0.6 mmol) and HBTU (226 mg, 0.6 mmol). The peptide resin was carried through steps 1 - 5 of protocol 1, washed with CH_2Cl_2 (three times) and treated with 1 ml of butyric anhydride in 6% DIPEA/CH_2Cl_2 for 30 minutes. The resin was filtered and washed successively with 20 ml each of CH_2Cl_2 (two times), isopropanol, and CH_2Cl_2 (three times). The resin was dried under vacuum to yield 590mg of butyl Pentapeptide resin.

The butyl Pentapeptide resin was treated with 40 µL ethanedithiol, 40 µL dimethylsulfide, 120 µL anisole, and 4 mL trifluoroacetic acid at room temperature for 180 min. The resin was filtered off, washed with ~2 ml TFA and the filtrates precipitated in chilled ethyl ether. The precipitates were centrifuged and the ether layer decanted. The residue was washed with two or three volumes of Et_2O and recentrifuged and the crude product was dried under vacuum to yield 140 mg of an off-white solid.

This crude material was purified by preparative HPLC on a Vydac C18-column (2.5 x 20 cm) and eluted with a linear gradient of 10-60% B (buffer A: 0.1% TFA/H_2O, buffer B: 0.1% TFA/CH_3CN) in 60 min., flow rate 8ml/min, detection 280 nm. The main peak was cut by analytical HPLC analysis of collected fractions, pooled and lyophilized to yield 30 mg (16 %) of a white, amorphous powder. This compound was homogeneous by HPLC. LR-Electrospray: $C_{50}H_{56}N_9O_6Br$, cal: 959 observed: m/z (960 M+H).

EXAMPLE 101

Penta-**Appc**-(D)Phe-Arg-Trp-Gly-NH_2



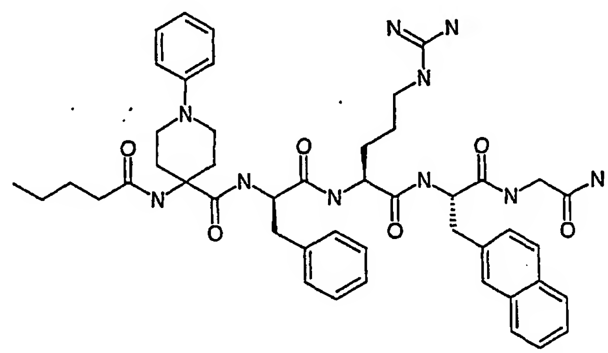
Fmoc-Linker-BHA resin (360 mg, 0.2 mmol) from Example 29 were subjected to solid phase synthesis using protocol 1 described above. All couplings were performed using HBTU in DMF as the coupling agent and DIPEA (3 equiv.) as base. Five coupling cycles were performed of one cycle each with Fmoc-Gly (180 mg, 0.6 mmol) and HBTU (226 mg, 0.6 mmol), Fmoc-Trp (260 mg, 0.6 mmol) and HBTU (226 mg, 0.6 mmol), Fmoc-Arg (Pmc) (400 mg, 0.6 mmol) and HBTU (226 mg, 0.6 mmol), Fmoc-(D)Phe (240 mg, 0.6 mmol) and HBTU (226 mg, 0.6 mmol), **Fmoc-Appc** (275 mg 0.6 mmol) and HBTU (226 mg, 0.6 mmol). The peptide resin was carried through steps 1 - 5 of protocol 1, washed with CH_2Cl_2 (three times) and treated with 1 mL valeric anhydride in 6% DIPEA/CH_2Cl_2 for 30 minutes. The resin was filtered and washed successively with 20 ml each of CH_2Cl_2 (two times), isopropanol, and CH_2Cl_2 (three times). The resin was dried under vacuum to yield 620 mg of Pentyl-Pentapeptide resin.

The Pentyl-Pentapeptide resin was treated with 40 μL ethanedithiol, 40 μL dimethylsulfide, 120 μL anisole, and 4 mL trifluoroacetic acid at room temperature for 180 min. The resin was filtered off, washed with ~2 ml TFA and the filtrates precipitated in chilled ethyl ether. The precipitates were centrifuged and the ether layer decanted. The residue was washed with two or three volumes of Et_2O and recentrifuged and the crude product was dried under vacuum to yield 153 mg of an off-white solid.

This crude material was purified by preparative HPLC on a Vydac C18-column (2.5 x 20 cm) and eluted with a linear gradient of 10-60% B (buffer A: 0.1% TFA/H_2O, buffér B: 0.1% TFA/CH_3CN) in 60 min., flow rate 8ml/min, detection 280 nm. The main peak was cut by analytical HPLC analysis of collected fractions, pooled and lyophilized to yield 65 mg (38 %) of a white, amorphous powder. This compound was homogeneous by HPLC. LR-Electrospray: $C_{45}H_{59}N_{11}O_6$, cal: 850 observed: m/z (851 M+H).

EXAMPLE 102

Penta-Appc-(D)Phe-Arg-(2)Nal-Gly-NH_2



Fmoc-Linker-BHA resin (360 mg, 0.2 mmol) from Example 29 were subjected to solid phase synthesis using protocol 1 described above. All couplings were performed using HBTU in DMF as the coupling agent and DIPEA (3 equiv.) as base. Five coupling cycles were performed of one cycle each with Fmoc-Gly (180 mg, 0.6 mmol) and HBTU (226 mg, 0.6 mmol), **Fmoc-(2)Nal** (265 mg, 0.6 mmol) and HBTU (226 mg, 0.6 mmol), Fmoc-Arg (Pmc)

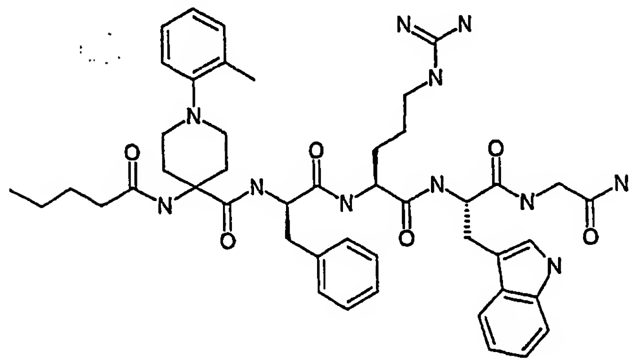
(400 mg, 0.6 mmol) and HBTU (226 mg, 0.6 mmol), Fmoc-(D)Phe (240 mg, 0.6 mmol) and HBTU (226 mg, 0.6 mmol), **Fmoc-Appc** (275 mg 0.6 mmol) and HBTU (226 mg, 0.6 mmol). The peptide resin was carried through steps 1 - 5 of protocol 1, washed with CH_2Cl_2 (three times) and treated with 1 mL valeric anhydride in 6% DIPEA/CH_2Cl_2 for 30 minutes. The resin was filtered and washed successively with 20 ml each of CH_2Cl_2 (two times), isopropanol, and CH_2Cl_2 (three times). The resin was dried under vacuum to yield 610 mg of Pentyl-Pentapeptide resin.

The Pentyl-Pentapeptide resin was treated with 40 µL ethanedithiol, 40 µL dimethylsulfide, 120 µL anisole, and 4 mL trifluoroacetic acid at room temperature for 180 min. The resin was filtered off, washed with ~2 ml TFA and the filtrates precipitated in chilled ethyl ether. The precipitates were centrifuged and the ether layer decanted. The residue was washed with two or three volumes of Et_2O and recentrifuged and the crude product was dried under vacuum to yield 145 mg of an off-white solid.

This crude material was purified by preparative HPLC on a Vydac C18-column (2.5 x 20 cm) and eluted with a linear gradient of 10-60% B (buffer A: 0.1% TFA/H_2O, buffer B: 0.1% TFA/CH_3CN) in 60 min., flow rate 8ml/min, detection 280 nm. The main peak was cut by analytical HPLC analysis of collected fractions, pooled and lyophilized to yield 55 mg (32 %) of a white, amorphous powder. This compound was homogeneous by HPLC. LR-Electrospray: $C_{47}H_{60}N_{10}O_6$, cal: 861 observed: m/z (862 M+H).

EXAMPLE 103

Penta-2-MeAppc-(D)Phe-Arg-Trp-Gly-NH_2



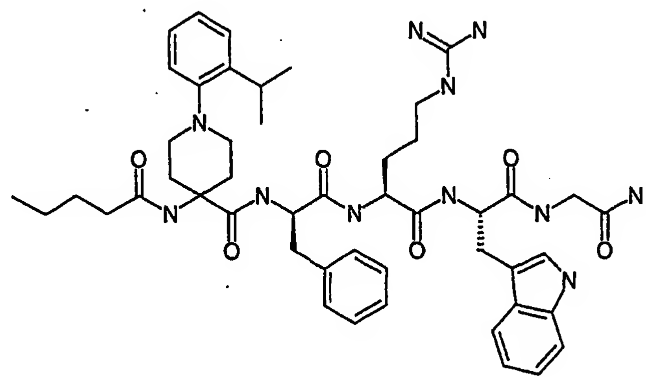
Fmoc-Linker-BHA resin (360 mg, 0.2 mmol) from Example 29 were subjected to solid phase synthesis using protocol 1 described above. All couplings were performed using HBTU in DMF as the coupling agent and DIPEA (3 equiv.) as base. Five coupling cycles were performed of one cycle each with Fmoc-Gly (180 mg, 0.6 mmol) and HBTU (226 mg, 0.6 mmol), Fmoc-Trp (260 mg, 0.6 mmol) and HBTU (226 mg, 0.6 mmol), Fmoc-Arg (Pmc) (400 mg, 0.6 mmol) and HBTU (226 mg, 0.6 mmol), Fmoc-(D)Phe (240 mg, 0.6 mmol) and HBTU (226 mg, 0.6 mmol), **Fmoc-2-MeAppc** (285 mg 0.6 mmol) and HBTU (226 mg, 0.6 mmol). The peptide resin was carried through steps 1 - 5 of protocol 1, washed with CH_2Cl_2 (three times) and treated with 1 mL valeric anhydride in 6% DIPEA/CH_2Cl_2 for 30 minutes. The resin was filtered and washed successively with 20 ml each of CH_2Cl_2 (two times), isopropanol, and CH_2Cl_2 (three times). The resin was dried under vacuum to yield 580 mg of Pentyl-Pentapeptide resin.

The Pentyl-Pentapeptide resin was treated with 40 μL ethanedithiol, 40 μL dimethylsulfide, 120 μL anisole, and 4 mL trifluoroacetic acid at room temperature for 180 min. The resin was filtered off, washed with ~2 ml TFA and the filtrates precipitated in chilled ethyl ether. The precipitates were centrifuged and the ether layer decanted. The residue was washed with two or three volumes of Et_2O and recentrifuged and the crude product was dried under vacuum to yield 145 mg of an off-white solid.

This crude material was purified by preparative HPLC on a Vydac C18-column (2.5 x 20 cm) and eluted with a linear gradient of 10-60% B (buffer A: 0.1% TFA/H_2O, buffer B: 0.1% TFA/CH_3CN) in 60 min., flow rate 8ml/min, detection 280 nm. The main peak was cut by analytical HPLC analysis of collected fractions, pooled and lyophilized to yield 59 mg (35 %) of a white, amorphous powder. This compound was homogeneous by HPLC. LR-Electrospray: $C_{46}H_{61}N_{11}O_6$, cal: 864 observed: m/z (865 M+H).

EXAMPLE 104

Penta-**2-iPrAppc**-(D)Phe-Arg-Trp-Gly-NH_2



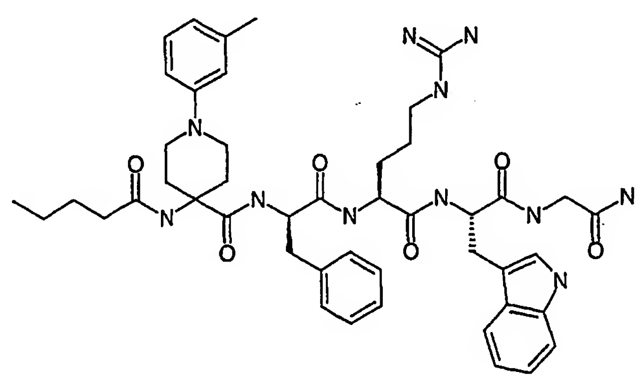
Fmoc-Linker-BHA resin (360 mg, 0.2 mmol) from Example 29 were subjected to solid phase synthesis using protocol 1 described above. All couplings were performed using HBTU in DMF as the coupling agent and DIPEA (3 equiv.) as base. Five coupling cycles were performed of one cycle each with Fmoc-Gly (180 mg, 0.6 mmol) and HBTU (226 mg, 0.6 mmol), Fmoc-Trp (260 mg, 0.6 mmol) and HBTU (226 mg, 0.6 mmol), Fmoc-Arg (Pmc) (400 mg, 0.6 mmol) and HBTU (226 mg, 0.6 mmol), Fmoc-(D)Phe (240 mg, 0.6 mmol) and HBTU (226 mg, 0.6 mmol), **Fmoc-2-iPrAppc** (295 mg 0.6 mmol) and HBTU (226 mg, 0.6 mmol). The peptide resin was carried through steps 1 - 5 of protocol 1, washed with CH_2Cl_2 (three times) and treated with 1 mL valeric anhydride in 6% DIPEA/CH_2Cl_2 for 30 minutes. The resin was filtered and washed successively with 20 ml each of CH_2Cl_2 (two times), isopropanol, and CH_2Cl_2 (three times). The resin was dried under vacuum to yield 600 mg of Pentyl-Pentapeptide resin.

The Pentyl-Pentapeptide resin was treated with 40 µL ethanedithiol, 40 µL dimethylsulfide, 120 µL anisole, and 4 mL trifluoroacetic acid at room temperature for 180 min. The resin was filtered off, washed with ~2 ml TFA and the filtrates precipitated in chilled ethyl ether. The precipitates were centrifuged and the ether layer decanted. The residue was washed with two or three volumes of Et_2O and recentrifuged and the crude product was dried under vacuum to yield 147 mg of an off-white solid.

This crude material was purified by preparative HPLC on a Vydac C18-column (2.5 x 20 cm) and eluted with a linear gradient of 10-60% B (buffer A: 0.1% TFA/H_2O, buffér B: 0.1% TFA/CH_3CN) in 60 min., flow rate 8ml/min, detection 280 nm. The main peak was cut by analytical HPLC analysis of collected fractions, pooled and lyophilized to yield 49 mg (27 %) of a white, amorphous powder. This compound was homogeneous by HPLC. LR-Electrospray: $C_{48}H_{65}N_{11}O_6$, cal: 892 observed: m/z (893 M+H).

EXAMPLE 105

Penta-3-MeAppc-(D)Phe-Arg-Trp-Gly-NH_2



Fmoc-Linker-BHA resin (360 mg, 0.2 mmol) from Example 29 were subjected to solid phase synthesis using protocol 1 described above. All couplings were performed using HBTU in DMF as the coupling agent and DIPEA (3 equiv.) as base. Five coupling cycles were performed of one cycle each with Fmoc-Gly (180 mg, 0.6 mmol) and HBTU (226 mg, 0.6 mmol), Fmoc-Trp (260 mg, 0.6 mmol) and HBTU (226 mg, 0.6 mmol), Fmoc-Arg (Pmc) (400 mg, 0.6 mmol) and HBTU (226 mg, 0.6 mmol), Fmoc-(D)Phe (240 mg, 0.6 mmol) and

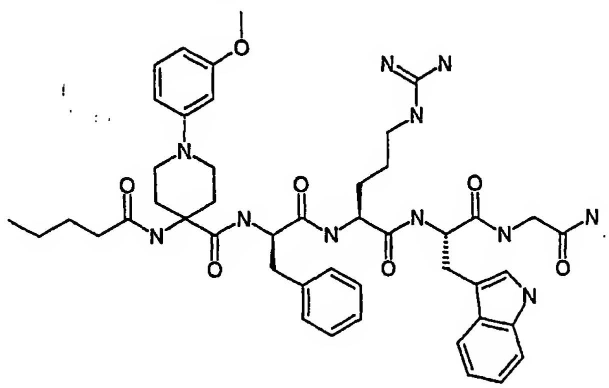
HBTU (226 mg, 0.6 mmol), **Fmoc-3-MeAppc** (285 mg 0.6 mmol) and HBTU (226 mg, 0.6 mmol). The peptide resin was carried through steps 1 - 5 of protocol 1, washed with CH_2Cl_2 (three times) and treated with 1 mL valeric anhydride in 6% DIPEA/CH_2Cl_2 for 30 minutes. The resin was filtered and washed successively with 20 ml each of CH_2Cl_2 (two times), isopropanol, and CH_2Cl_2 (three times). The resin was dried under vacuum to yield 595 mg of Pentyl-Pentapeptide resin.

The Pentyl-Pentapeptide resin was treated with 40 µL ethanedithiol, 40 µL dimethylsulfide, 120 µL anisole, and 4 mL trifluoroacetic acid at room temperature for 180 min. The resin was filtered off, washed with ~2 ml TFA and the filtrates precipitated in chilled ethyl ether. The precipitates were centrifuged and the ether layer decanted. The residue was washed with two or three volumes of Et_2O and recentrifuged and the crude product was dried under vacuum to yield 140 mg of an off-white solid.

This crude material was purified by preparative HPLC on a Vydac C18-column (2.5 x 20 cm) and eluted with a linear gradient of 10-60% B (buffer A: 0.1% TFA/H_2O, buffer B: 0.1% TFA/CH_3CN) in 60 min., flow rate 8ml/min, detection 280 nm. The main peak was cut by analytical HPLC analysis of collected fractions, pooled and lyophilized to yield 55 mg (32 %) of a white, amorphous powder. This compound was homogeneous by HPLC. LR-Electrospray: $C_{46}H_{61}N_{11}O_6$, cal: 864 observed: m/z (865 M+H).

EXAMPLE 106

Penta-3-MeOAppc-(D)Phe-Arg-Trp-Gly-NH_2



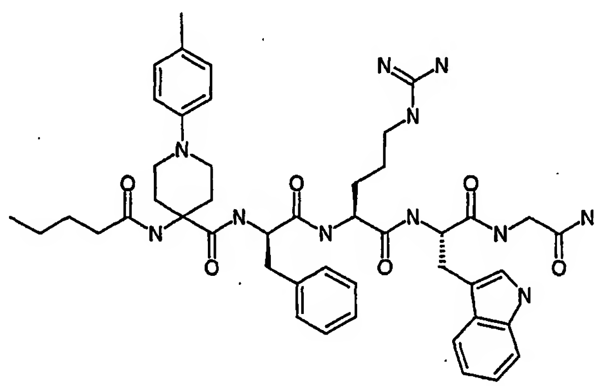
Fmoc-Linker-BHA resin (360 mg, 0.2 mmol) from Example 29 were subjected to solid phase synthesis using protocol 1 described above. All couplings were performed using HBTU in DMF as the coupling agent and DIPEA (3 equiv.) as base. Five coupling cycles were performed of one cycle each with Fmoc-Gly (180 mg, 0.6 mmol) and HBTU (226 mg, 0.6 mmol), Fmoc-Trp (260 mg, 0.6 mmol) and HBTU (226 mg, 0.6 mmol), Fmoc-Arg (Pmc) (400 mg, 0.6 mmol) and HBTU (226 mg, 0.6 mmol), Fmoc-(D)Phe (240 mg, 0.6 mmol) and HBTU (226 mg, 0.6 mmol), **Fmoc-3-MeOAppc** (290 mg 0.6 mmol) and HBTU (226 mg, 0.6 mmol). The peptide resin was carried through steps 1 - 5 of protocol 1, washed with CH_2Cl_2 (three times) and treated with 1 mL valeric anhydride in 6% DIPEA/CH_2Cl_2 for 30 minutes. The resin was filtered and washed successively with 20 ml each of CH_2Cl_2 (two times), isopropanol, and CH_2Cl_2 (three times). The resin was dried under vacuum to yield 600 mg of Pentyl-Pentapeptide resin.

The Pentyl-Pentapeptide resin was treated with 40 μL ethanedithiol, 40 μL dimethylsulfide, 120 μL anisole, and 4 mL trifluoroacetic acid at room temperature for 180 min. The resin was filtered off, washed with ~2 ml TFA and the filtrates precipitated in chilled ethyl ether. The precipitates were centrifuged and the ether layer decanted. The residue was washed with two or three volumes of Et_2O and recentrifuged and the crude product was dried under vacuum to yield 154 mg of an off-white solid.

This crude material was purified by preparative HPLC on a Vydac C18-column (2.5 x 20 cm) and eluted with a linear gradient of 10-60% B (buffer A: 0.1% TFA/H_2O, buffer B: 0.1% TFA/CH_3CN) in 60 min., flow rate 8ml/min, detection 280 nm. The main peak was cut by analytical HPLC analysis of collected fractions, pooled and lyophilized to yield 50 mg (29 %) of a white, amorphous powder. This compound was homogeneous by HPLC. LR-Electrospray: $C_{46}H_{61}N_{11}O_7$, cal: 880 observed: m/z (881 M+H).

EXAMPLE 107

Penta-**4-MeAppc**-(D)Phe-Arg-Trp-Gly-NH_2



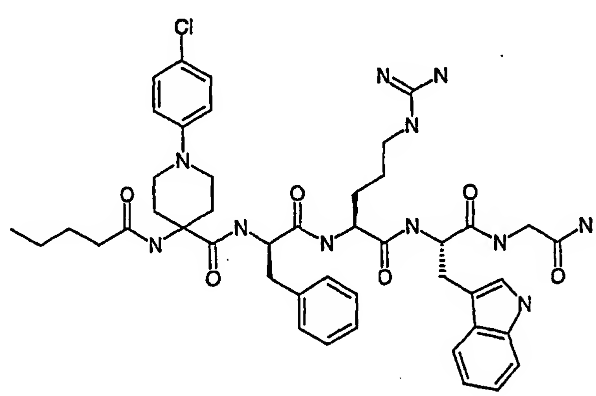
Fmoc-Linker-BHA resin (360 mg, 0.2 mmol) from Example 29 were subjected to solid phase synthesis using protocol 1 described above. All couplings were performed using HBTU in DMF as the coupling agent and DIPEA (3 equiv.) as base. Five coupling cycles were performed of one cycle each with Fmoc-Gly (180 mg, 0.6 mmol) and HBTU (226 mg, 0.6 mmol), Fmoc-Trp (260 mg, 0.6 mmol) and HBTU (226 mg, 0.6 mmol), Fmoc-Arg (Pmc) (400 mg, 0.6 mmol) and HBTU (226 mg, 0.6 mmol), Fmoc-(D)Phe (240 mg, 0.6 mmol) and HBTU (226 mg, 0.6 mmol), **Fmoc-4-MeAppc** (285 mg 0.6 mmol) and HBTU (226 mg, 0.6 mmol). The peptide resin was carried through steps 1 - 5 of protocol 1, washed with CH_2Cl_2 (three times) and treated with 1 mL valeric anhydride in 6% DIPEA/CH_2Cl_2 for 30 minutes. The resin was filtered and washed successively with 20 ml each of CH_2Cl_2 (two times), isopropanol, and CH_2Cl_2 (three times). The resin was dried under vacuum to yield 600 mg of Pentyl-Pentapeptide resin.

The Pentyl-Pentapeptide resin was treated with 40 μL ethanedithiol, 40 μL dimethylsulfide, 120 μL anisole, and 4 mL trifluoroacetic acid at room temperature for 180 min. The resin was filtered off, washed with ~2 ml TFA and the filtrates precipitated in chilled ethyl ether. The precipitates were centrifuged and the ether layer decanted. The residue was washed with two or three volumes of Et_2O and recentrifuged and the crude product was dried under vacuum to yield 150 mg of an off-white solid.

This crude material was purified by preparative HPLC on a Vydac C18-column (2.5 x 20 cm) and eluted with a linear gradient of 10-60% B (buffer A: 0.1% TFA/H_2O, buffer B: 0.1% TFA/CH_3CN) in 60 min., flow rate 8ml/min, detection 280 nm. The main peak was cut by analytical HPLC analysis of collected fractions, pooled and lyophilized to yield 57 mg (33 %) of a white, amorphous powder. This compound was homogeneous by HPLC. LR-Electrospray: $C_{46}H_{61}N_{11}O_6$, cal: 864 observed: m/z (865 M+H).

EXAMPLE 108

Penta-4-ClAppc-(D)Phe-Arg-Trp-Gly-NH_2



Fmoc-Linker-BHA resin (360 mg, 0.2 mmol) from Example 29 were subjected to solid phase synthesis using protocol 1 described above. All couplings were performed using HBTU in DMF as the coupling agent and DIPEA (3 equiv.) as base. Five coupling cycles were performed of one cycle each with Fmoc-Gly (180 mg, 0.6 mmol) and HBTU (226 mg, 0.6 mmol), Fmoc-Trp (260 mg, 0.6 mmol) and HBTU (226 mg, 0.6 mmol), Fmoc-Arg (Pmc)

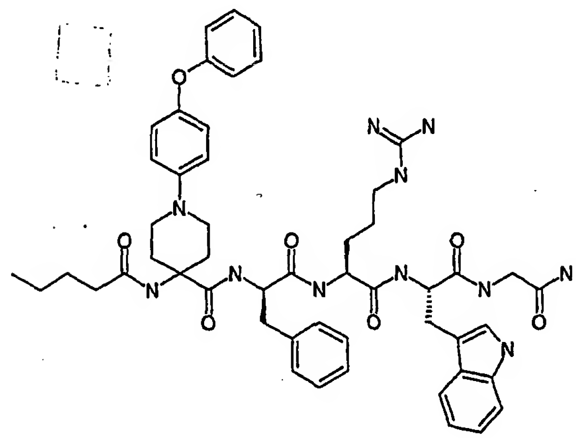
(400 mg, 0.6 mmol) and HBTU (226 mg, 0.6 mmol), Fmoc-(D)Phe (240 mg, 0.6 mmol) and HBTU (226 mg, 0.6 mmol), **Fmoc-4-ClAppc** (290 mg 0.6 mmol) and HBTU (226 mg, 0.6 mmol). The peptide resin was carried through steps 1 - 5 of protocol 1, washed with CH_2Cl_2 (three times) and treated with 1 mL valeric anhydride in 6% DIPEA/CH_2Cl_2 for 30 minutes. The resin was filtered and washed successively with 20 ml each of CH_2Cl_2 (two times), isopropanol, and CH_2Cl_2 (three times). The resin was dried under vacuum to yield 580 mg of Pentyl-Pentapeptide resin.

The Pentyl-Pentapeptide resin was treated with 40 µL ethanedithiol, 40 µL dimethylsulfide, 120 µL anisole, and 4 mL trifluoroacetic acid at room temperature for 180 min. The resin was filtered off, washed with ~2 ml TFA and the filtrates precipitated in chilled ethyl ether. The precipitates were centrifuged and the ether layer decanted. The residue was washed with two or three volumes of Et_2O and recentrifuged and the crude product was dried under vacuum to yield 140 mg of an off-white solid.

This crude material was purified by preparative HPLC on a Vydac C18-column (2.5 x 20 cm) and eluted with a linear gradient of 10-60% B (buffer A: 0.1% TFA/H_2O, buffer B: 0.1% TFA/CH_3CN) in 60 min., flow rate 8ml/min, detection 280 nm. The main peak was cut by analytical HPLC analysis of collected fractions, pooled and lyophilized to yield 49 mg (28 %) of a white, amorphous powder. This compound was homogeneous by HPLC. LR-Electrospray: $C_{45}H_{58}N_{11}O_6Cl$, cal: 884 observed: m/z (885 M+H).

EXAMPLE 109

Penta-**4-PhOAppc**-(D)Phe-Arg-Trp-Gly-NH_2



Fmoc-Linker-BHA resin (360 mg, 0.2 mmol) from Example 29 were subjected to solid phase synthesis using protocol 1 described above. All couplings were performed using HBTU in DMF as the coupling agent and DIPEA (3 equiv.) as base. Five coupling cycles were performed of one cycle each with Fmoc-Gly (180 mg, 0.6 mmol) and HBTU (226 mg, 0.6 mmol), Fmoc-Trp (260 mg, 0.6 mmol) and HBTU (226 mg, 0.6 mmol), Fmoc-Arg (Pmc) (400 mg, 0.6 mmol) and HBTU (226 mg, 0.6 mmol), Fmoc-(D)Phe (240 mg, 0.6 mmol) and HBTU (226 mg, 0.6 mmol), **Fmoc-4-PhOAppc** (325 mg 0.6 mmol) and HBTU (226 mg, 0.6 mmol). The peptide resin was carried through steps 1 - 5 of protocol 1, washed with CH_2Cl_2 (three times) and treated with 1 mL valeric anhydride in 6% DIPEA/CH_2Cl_2 for 30 minutes. The resin was filtered and washed successively with 20 ml each of CH_2Cl_2 (two times), isopropanol, and CH_2Cl_2 (three times). The resin was dried under vacuum to yield 610 mg of Pentyl-Pentapeptide resin.

The Pentyl-Pentapeptide resin was treated with 40 µL ethanedithiol, 40 µL dimethylsulfide, 120 µL anisole, and 4 mL trifluoroacetic acid at room temperature for 180 min. The resin was filtered off, washed with ~2 ml TFA and the filtrates precipitated in chilled ethyl ether. The precipitates were centrifuged and the ether layer decanted. The

residue was washed with two or three volumes of Et_2O and recentrifuged and the crude product was dried under vacuum to yield 143 mg of an off-white solid.

This crude material was purified by preparative HPLC on a Vydac C18-column (2.5 x 20 cm) and eluted with a linear gradient of 10-60% B (buffer A: 0.1% TFA/H_2O, buffer B: 0.1% TFA/CH_3CN) in 60 min., flow rate 8ml/min, detection 280 nm. The main peak was cut by analytical HPLC analysis of collected fractions, pooled and lyophilized to yield 41 mg (22 %) of a white, amorphous powder. This compound was homogeneous by HPLC. LR-Electrospray: $C_{51}H_{63}N_{11}O_7$, cal: 942 observed: m/z (943 M+H).

BIOLOGICAL ACTIVITY EXAMPLE:

Example A: Agonist Assay

Method

Description: 293 cells (ATCC CRL-1573) were transfected with DNA constructs comprising either the MC-4 receptor DNA or the MC-1 receptor DNA and grown in 96 well plates. MC-4 and MC-1 encoding DNA and the corresponding protein sequences are known in the art and described e.g. in Cone, et al., Rec. Prog. Hormone Res: (1996) 51: 287-318. The cells were stimulated with either 100nM NDP-αMSH or screening compounds. Cyclic AMP was extracted from the cells and concentrations were determined using a Biotrak-cAMP SPA assay. Agonists were identified as those compounds causing an increase in cAMP.

Cell Culture: 293MC4 cells (obtained as described above) were cultured in 75cm^{2}flasks in D-MEM supplemented with 10% FCS and 500µg/ml G418. Cells were trypsinized and split 1:3 into 96 well flat-bottom tissue culture treated plates. Cells were stimulated at confluence (day 2-4).

cAMP Response: Compounds serially diluted in 100% DMSO were further diluted 1:200 (2.5μl compound dilution + 500μl media) in D-MEM containing 10%FBS and 0.1mM IBMX. For unstimulated cells, 2.5μl of DMSO was added to 500μl of media. For NDP-αMSH stimulated cells, 2.5μl of 20μM NDP-αMSH in 100% DMSO was added to 500μl of media (final conc. 100nM).

Final concentration of DMSO in all wells was 0.5%.

Note: Each sample was run in duplicate on separate plates

Culture medium was removed from confluent 96 well culture plates and replaced with 200μl of above dilutions into the appropriate wells . The plates were incubated for 1hr at RT. The media was removed, and the plates were washed 1x with 200μl well of PBS. CAMP was extracted by the addition of 60μl 70% ethanol (stored in the refrigerator). After a 30min extraction period, 10μl ethanol extract was transferred to the cAMP assay plate or samples were stored at -20°C until the cAMP assay was performed.

cAMP Assay: The extracted samples and all reagents included in the kit were brought to room temperature. To a 96 well OptiPlate, 10μl ethanol extract, 40μl assay buffer, 50ul [125I]cAMP, 50μl antiserum and 50μl SPA beads were added. The total well volume after addition was 200μl. The plates were sealed and incubated for 15-20 hr at room temperature. [125I]cAMP binding to the SPA beads was determined by counting each plate for 2 minutes on a Packard TopCount™.

Note: Each plate contained samples of controls for unstimulated cells and NDP-αMSH for stimulated cells.

Example A

Tablets containing the following ingredients can be manufactured in a conventional manner:

Ingredients	Per tablet
Compound of formula I	10.0 - 100.0 mg
Lactose	125.0 mg
Maize starch	75.0 mg
Talc	4.0 mg
Magnesium stearate	1.0 mg

Example B

Capsules containing the following ingredients can be manufactured in a conventional manner:

Ingredients	Per capsule
Compound of formula I	25.0 mg
Lactose	150.0 mg
Maize starch	20.0 mg
Talc	5.0 mg

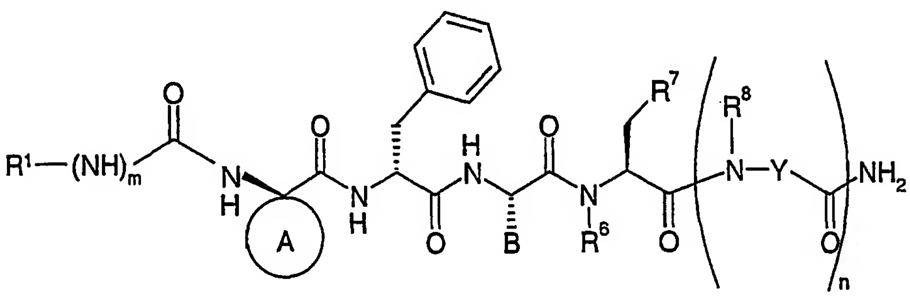
Example C

Injection solutions can have the following composition:

Compound of formula I	3.0 mg
Gelatine	150.0 mg
Phenol	4.7 mg
Water for injection solutions	ad 1.0 ml

Claims

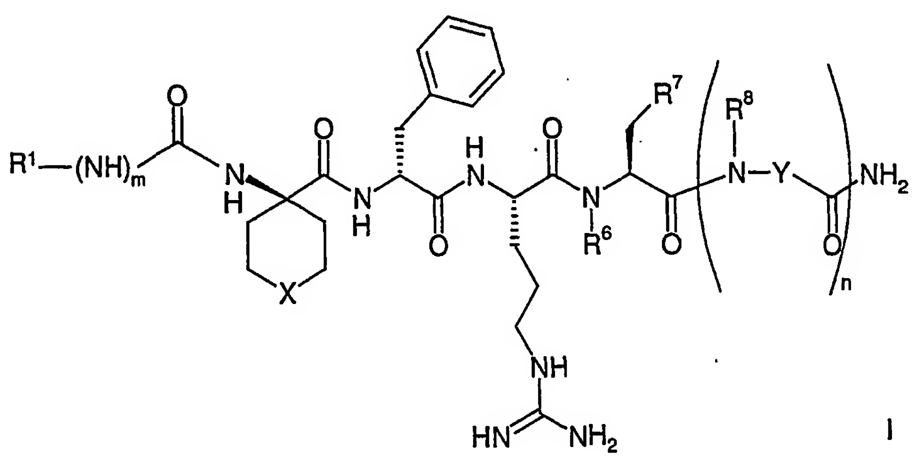
1. A compound comprising the following structure (S1):



(S1)

wherein R^1, R^6, R^7, R^8, m, n, A and B are as defined in a) to d) and wherein the compound is selected from the group consisting of

a) a compound of the formula:



I

wherein

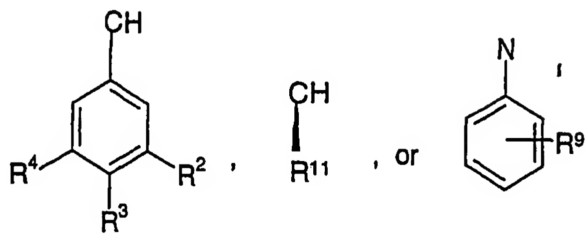
m is 0 or 1;

n is 0 or 1;

R^1 is an unsubstituted linear or branched alkyl having from 1 to 8 carbon atoms; linear or branched alkyl having from 1 to 8 carbon atoms mono-substituted by phenyl or carboxyl;

unsubstituted phenyl; or phenyl mono-substituted by fluoro, chloro or linear or branched alkyl having from 1 to 4 carbon atoms;

X is



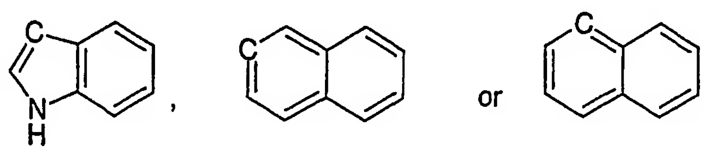
wherein R^2, R^3 and R^4 are independently hydrogen or a linear or branched alkoxy having from 1 to 4 carbon atoms, wherein when R^3 is alkoxy, R^2 and R^4 are both hydrogen;

R^9 is hydrogen, linear or branched alkyl having from 1 to 3 carbons, linear or branched alkoxy having from 1 to 3 carbons, or unsubstituted phenoxy;

R^{11} is cyclohexyl, cycloheptyl, or a branched alkyl having from 3 to 8 carbon atoms;

R^6 is hydrogen or methyl;

R^7 is

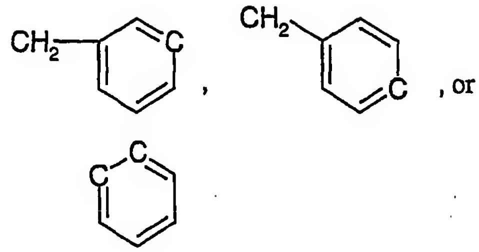


Y is

$$-CH_2-,\ -CH_2CH_2-,\ \text{or}\ -\overset{|}{C}H-CH_3,$$

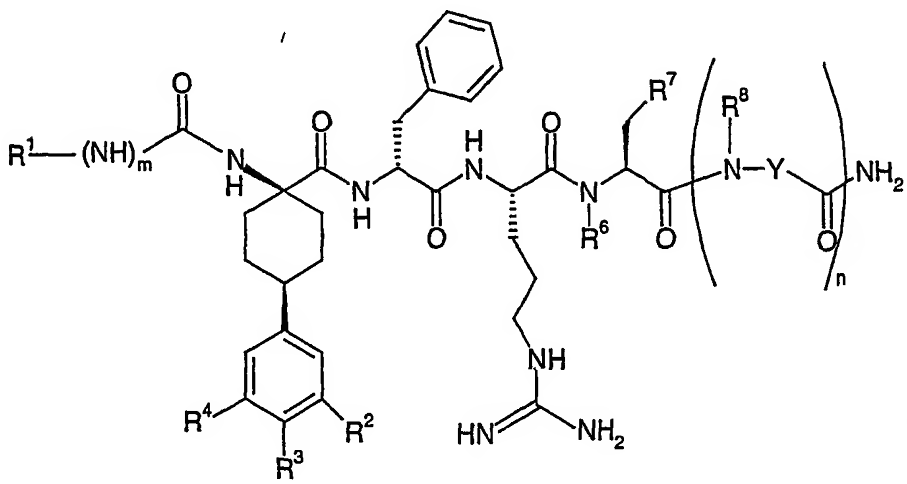
and R^8 is hydrogen or methyl; or

Y is



and R^8 is hydrogen;

b) a compound of the formula:



IA

wherein

m is 0 or 1;

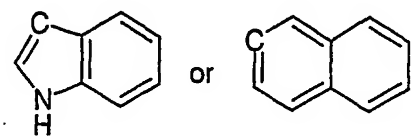
n is 0 or 1;

R^1 is an unsubstituted linear or branched alkyl having from 1 to 8 carbon atoms; linear or branched alkyl having from 1 to 8 carbon atoms mono-substituted by phenyl or carboxyl; unsubstituted phenyl; or phenyl mono-substituted by fluoro, chloro or linear or branched alkyl having from 1 to 4 carbon atoms;

R^2, R^3 and R^4 are independently hydrogen; a linear or branched alkyl having from 1 to 4 carbon atoms; hydroxy, a linear or branched alkoxy having from 1 to 4 carbon atoms; or chloro, wherein when R^3 is alkyl, hydroxy, alkoxy or chloro, R^2 and R^4 are both hydrogen;

R^6 is hydrogen or methyl;

R^7 is

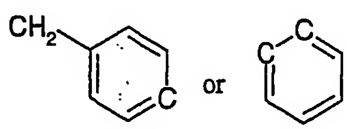


Y is

-CH$_2$-, -CH$_2$CH$_2$-, or -CH-CH$_3$,

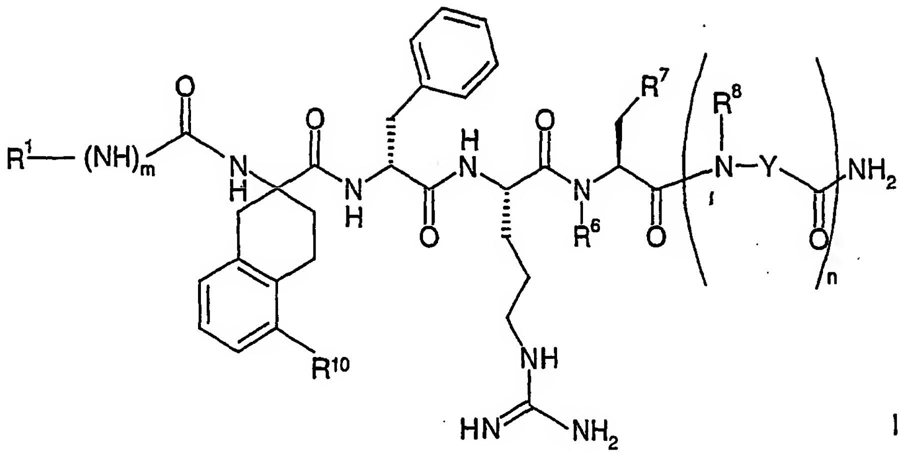
and R^8 is hydrogen or methyl; or

Y is



and R^8 is hydrogen;

c) a compound of the formula:



II

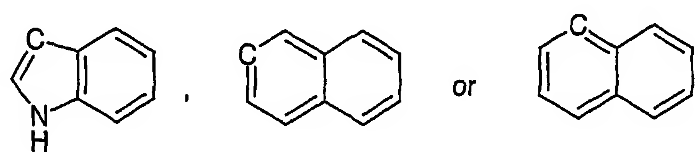
wherein

m is 0 or 1;

n is 0 or 1;

R^1 is an unsubstituted linear or branched alkyl having from 4 to 8 carbon atoms; linear or branched alkyl having from 1 to 8 carbon atoms mono-substituted by phenyl or carboxyl; or unsubstituted phenyl; or phenyl mono-substituted by fluoro, chloro or linear or branched alkyl having from 1 to 4 carbon atoms;

R^7 is

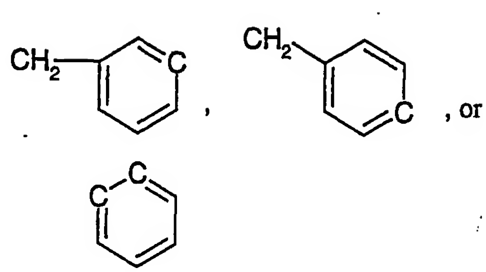


Y is

$$-CH_2-,\ -CH_2CH_2-,\ \text{or}\ -\overset{|}{C}H-CH_3,$$

and R^8 is hydrogen or methyl; or

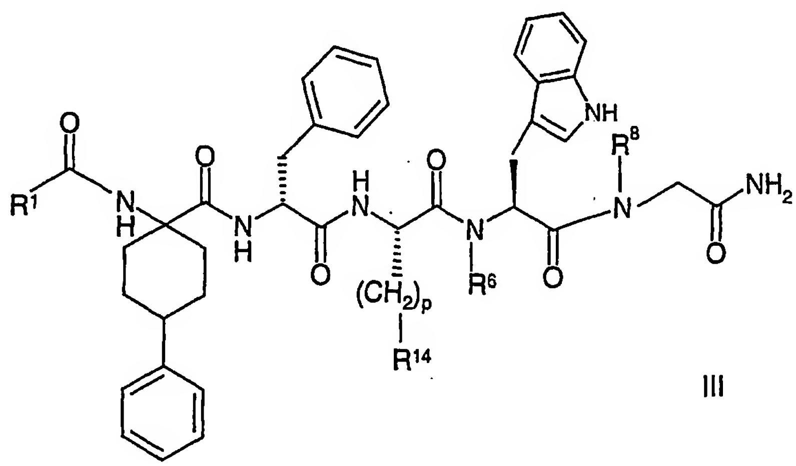
Y is



and R^8 is hydrogen;

R^{10} is hydrogen, halo, linear or branched alkyl having from 1 to 3 carbon atoms, linear or branched alkoxy having from 1 to 3 carbon atoms, or $-NR^{12}R^{13}$ wherein R^{12} and R^{13} are each independently a linear or branched alkyl having from 1 to 3 carbons or together are $-(CH_2)_q-$ wherein q is 3, 4 or 5; and

d) a compound of the formula:



III

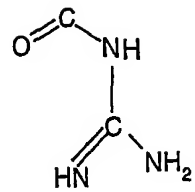
wherein

R^1 is unsubstituted linear or branched alkyl having from 4 to 8 carbon atoms;

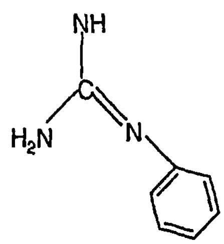
R^6 is hydrogen or methyl;

R^8 is hydrogen or methyl;

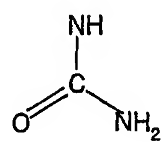
p is 2, 3 or 4 and R^{14} is


,

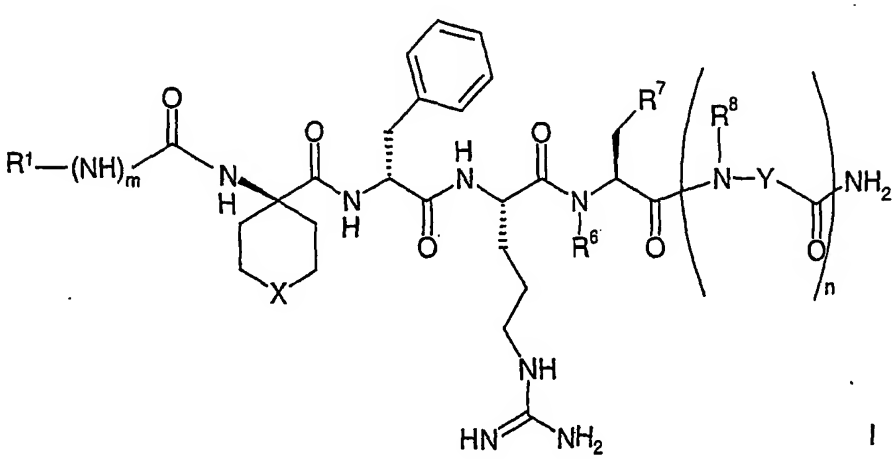
or p is 4 and R^{14} is


,

or p is 3 and R^{14} is


.

2. A compound according to claim 1 of the formula:



I

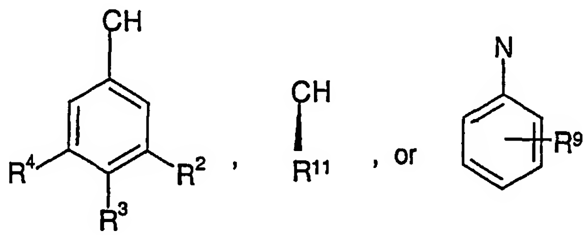
wherein

m is 0 or 1;

n is 0 or 1;

R^1 is an unsubstituted linear or branched alkyl having from 1 to 8 carbon atoms; linear or branched alkyl having from 1 to 8 carbon atoms mono-substituted by phenyl or carboxyl; unsubstituted phenyl; or phenyl mono-substituted by fluoro, chloro or linear or branched alkyl having from 1 to 4 carbon atoms;

X is



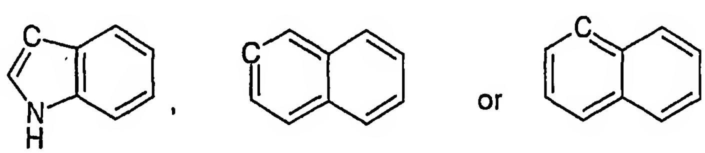
wherein R^2, R^3 and R^4 are independently hydrogen or a linear or branched alkoxy having from 1 to 4 carbon atoms, wherein when R^3 is alkoxy, R^2 and R^4 are both hydrogen;

R^9 is hydrogen, linear or branched alkyl having from 1 to 3 carbons, linear or branched alkoxy having from 1 to 3 carbons, or unsubstituted phenoxy;

R^{11} is cyclohexyl, cycloheptyl, or a branched alkyl having from 3 to 8 carbon atoms;

R^6 is hydrogen or methyl;

R^7 is

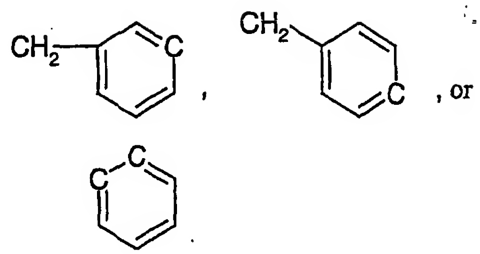


Y is

$$-CH_2-,\ -CH_2CH_2-,\ \text{or}\ -\overset{|}{C}H-CH_3,$$

and R^8 is hydrogen or methyl; or

Y is

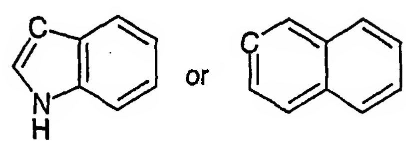


and R^8 is hydrogen.

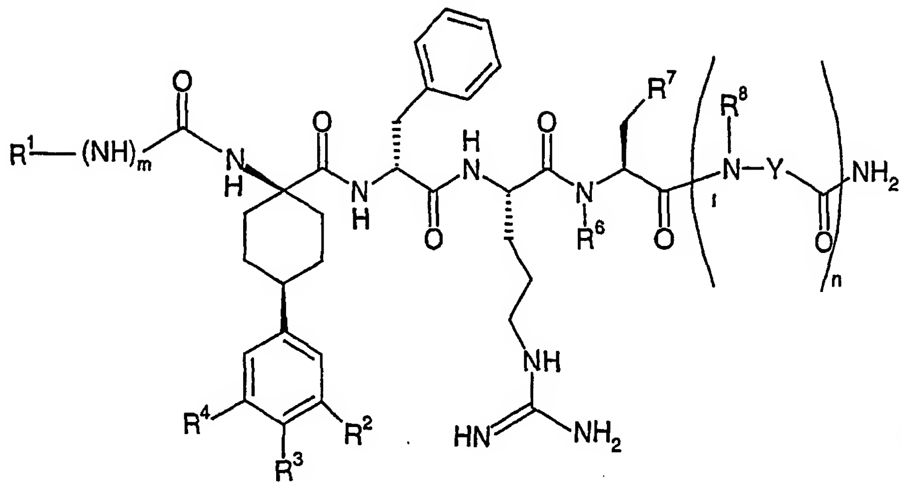
3. The compound of claim 2, wherein R^6 is hydrogen and R^8 is hydrogen.

4. The compound of claim 2, wherein n is 1.

5. The compound of claim 2, wherein R^7 is



6. A compound according to claim 1 of the formula:



IA

wherein

m is 0 or 1;

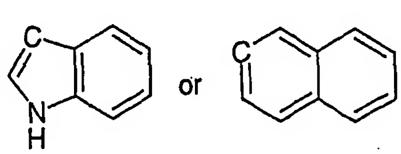
n is 0 or 1;

R^1 is an unsubstituted linear or branched alkyl having from 1 to 8 carbon atoms; linear or branched alkyl having from 1 to 8 carbon atoms mono-substituted by phenyl or carboxyl; unsubstituted phenyl; or phenyl mono-substituted by fluoro, chloro or linear or branched alkyl having from 1 to 4 carbon atoms;

R^2, R^3 and R^4 are independently hydrogen; a linear or branched alkyl having from 1 to 4 carbon atoms; hydroxy, a linear or branched alkoxy having from 1 to 4 carbon atoms; or chloro, wherein when R^3 is alkyl, hydroxy, alkoxy or chloro, R^2 and R^4 are both hydrogen;

R^6 is hydrogen or methyl;

R^7 is

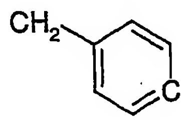
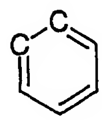


Y is

$-CH_2-$, $-CH_2CH_2-$, or $-\overset{|}{C}H-CH_3$,

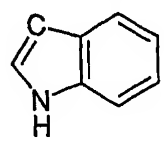
and R^8 is hydrogen or methyl; or

Y is

 or 

and R^8 is hydrogen.

7. The compound of claim 6, wherein R^7 is



8. The compound of claim 7, wherein n is 0.

9. The compound of claim 7, wherein n is 1.

10. The compound of claim 9, wherein Y is $-CH_2-$, CH_2CH_2-, or

$$-\overset{|}{C}H-CH_3.$$

11. The compound of claim 10, wherein m is 1.

12. The compound of claim 10, wherein m is 0.

13. The compound of claim 12, wherein R^2, R^3 and R^4 are hydrogen.

14. The compound of claim 13, wherein R^1 is unsubstituted linear alkyl.

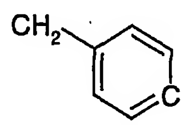
15. The compound of claim 13, wherein R^1 is unsubstituted phenyl.

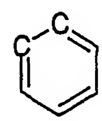
16. The compound of claim 12, wherein R^3 is alkyl, hydroxy, alkoxy or chloro.

17. The compound of claim 16, wherein R^3 is hydroxy or alkoxy.

18. The compound of claim 12, wherein R^2 is alkoxy, R^3 is hydrogen and R^4 is hydrogen.

19. The compound of claim 9, wherein Y is



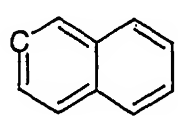
or


.

20. The compound of claim 19, wherein m is 1.

21. The compound of claim 19, wherein m is 0.

22. The compound of claim 6, wherein R^2, R^3 and R^4 are hydrogen and R^7 is



23. The compound of claim 22, wherein n is 1 and m is 0.

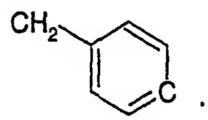
24. The compound of claim 23, where Y is $-CH_2$, $-CH_2CH_2-$, or

$$-\overset{|}{C}H-CH_3.$$

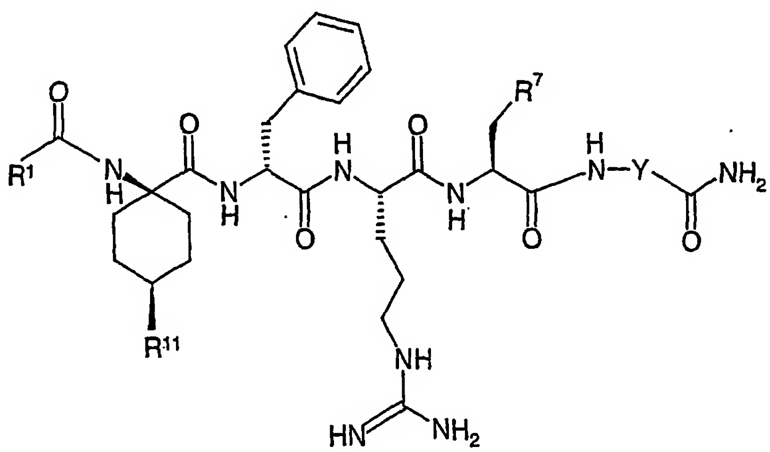
25. The compound of claim 24, wherein R^1 is an unsubstituted linear alkyl.

26. The compound of claim 24, wherein R^1 is unsubstituted phenyl; or alkyl substituted by phenyl or carboxyl.

27. The compound of claim 23, wherein R^1 is unsubstituted lower alkyl and Y is

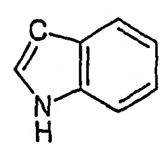


28. The compound of claim 2 of the formula:



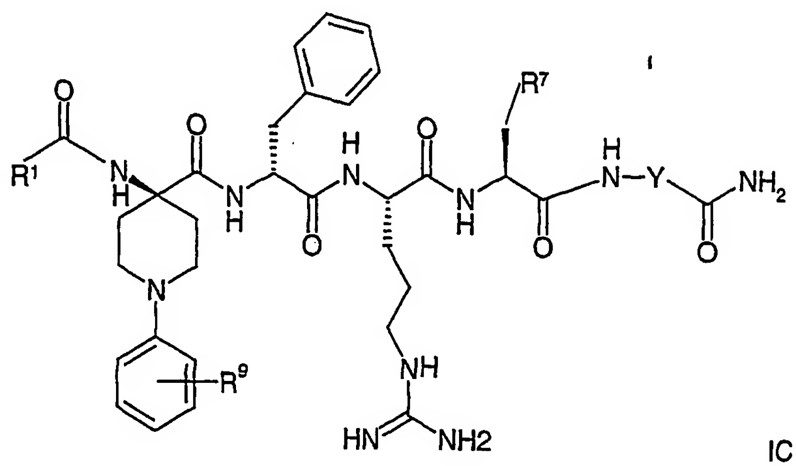
IB

R^1 is an unsubstituted linear or branched alkyl having from 1 to 8 carbon atoms;
R^7 is



R^{11} is cyclohexyl, or a branched alkyl having from 3 to 8 carbon atoms; and
Y is $-CH_2-$.

29. The compound of claim 2 of the formula:

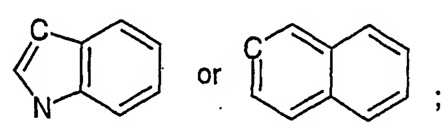


IC

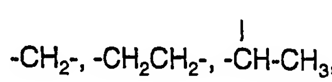
wherein

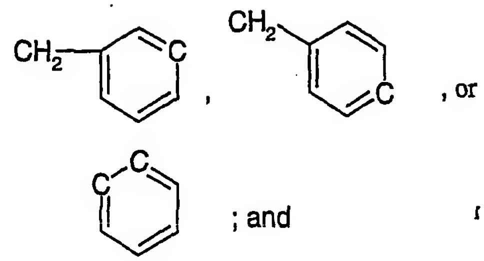
R^1 is an unsubstituted linear or branched alkyl having from 1 to 8 carbon atoms;

R^7 is



Y is





; and

R^9 is hydrogen, a linear or branched alkyl having from 1 to 3 carbon atoms, a linear or branched alkoxy having from 1 to 3 carbon atoms, fluoro, chloro, or unsubstituted phenoxy.

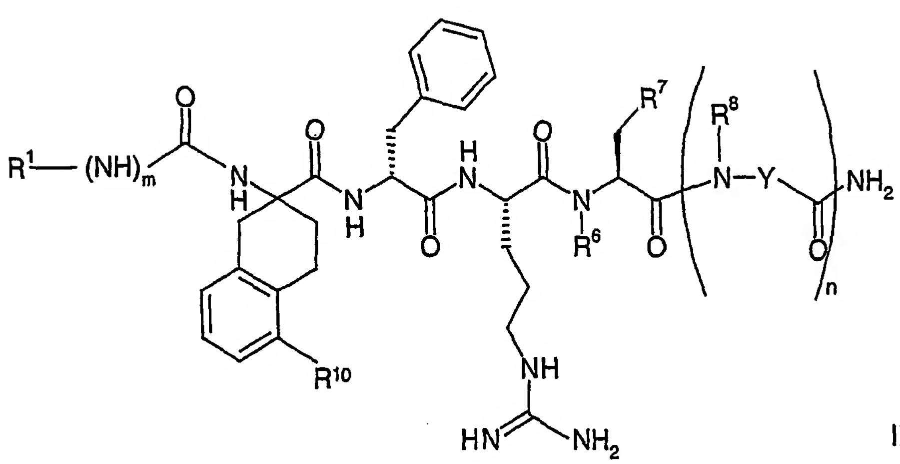
30. The compound of claim 29, wherein R^9 is hydrogen.

31. The compound of claim 29, wherein R^9 is a linear or branched alkyl having from 1 to 3 carbon atoms.

32. The compound of claim 29, wherein R^9 is a linear or branched alkoxy having from 1 to 3 carbon atoms, or unsubstituted phenoxy.

33. The compound of claim 29, wherein R^9 is chloro.

34. A compound according to claim 1 of the formula:



II

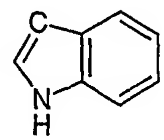
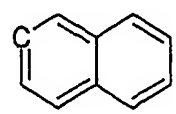
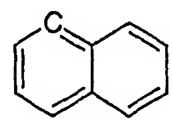
wherein

m is 0 or 1;

n is 0 or 1;

R^1 is an unsubstituted linear or branched alkyl having from 4 to 8 carbon atoms; linear or branched alkyl having from 1 to 8 carbon atoms mono-substituted by phenyl or carboxyl; or unsubstituted phenyl; or phenyl mono-substituted by fluoro, chloro or linear or branched alkyl having from 1 to 4 carbon atoms;

R^7 is

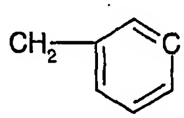
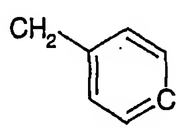
 ,  or 

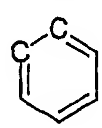
Y is

$-CH_2-$, $-CH_2CH_2-$, or $-\overset{|}{C}H-CH_3$,

and R^8 is hydrogen or methyl; or

Y is

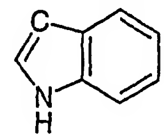
 ,  , or



and R^8 is hydrogen;

R^{10} is hydrogen, halo, linear or branched alkyl having from 1 to 3 carbon atoms, linear or branched alkoxy having from 1 to 3 carbon atoms, or $-NR^{12}R^{13}$ wherein R^{12} and R^{13} are each independently a linear or branched alkyl having from 1 to 3 carbons or together are $-(CH_2)_q-$ wherein q is 3, 4 or 5.

35. The compound of claim 34, wherein R^6 and R^8 are each hydrogen; R^7 is



and n is 1.

36. The compound of claim 35, wherein Y is $-CH_2-$ and m is 0.

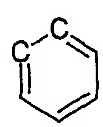
37. The compound of claim 36, wherein R^{10} is hydrogen, or a linear or branched alkyl having from 1 to 3 carbon atoms.

38. The compound of claim 36, wherein R^{10} is halo.

39. The compound of claim 36, wherein R^{10} is linear or branched alkoxy having from 1 to 3 carbon atoms.

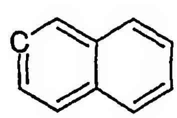
40. The compound of claim 36, wherein R^{10} is $-NR^{12}R^{13}$ and R^{12} and R^{13} are both methyl.

41. The compound of claim 35, wherein Y is



and R^{10} is halo.

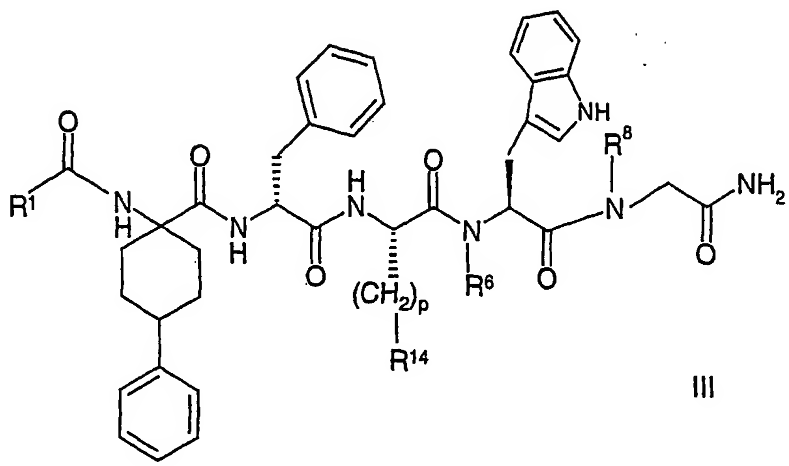
42. The compound of claim 34, wherein R^6 and R^8 are hydrogen; R^7 is



;

and R^{10} is halo.

43. A compound according to claim 1 of the formula:



III

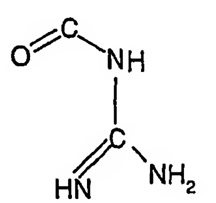
wherein

R^1 is unsubstituted linear or branched alkyl having from 4 to 8 carbon atoms;

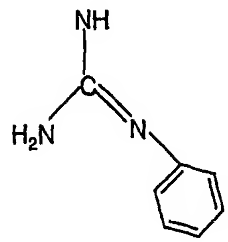
R^6 is hydrogen or methyl;

R^8 is hydrogen or methyl;

p is 2, 3 or 4 and R^{14} is

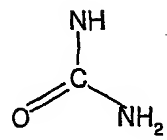


or p is 4 and R^{14} is



,

or p is 3 and R^{14} is



.

44. A compound according to any of claims 1 to 43, selected from the group consisting of
Penta-Apc-(D)Phe-Arg-Trp-Gly-NH_2,
Penta-4-MeOApc-(D)Phe-Arg-Trp-Gly-NH_2,
Penta-4-EtOApc-(D)Phe-Arg-Trp-Gly-NH_2,
Bu-Apc-(D)Phe-Arg-(2)Nal-beta-Ala-NH_2,
Penta-Apc-(D)Phe-Cit-Trp-Gly-NH_2,
Penta-Abc-(D)Phe-Arg-Trp-Gly-NH_2,
Penta-Achc-(D)Phe-Arg-Trp-Gly-NH_2,
Penta-5-BrAtc-(D)Phe-Arg-Trp-Gly-NH_2,
Penta-Appc-(D)Phe-Arg-Trp-Gly-NH_2, and
Penta-4-MeAppc-(D)Phe-Arg-Trp-Gly-NH_2.

45. A process for the preparation of compounds according to any of claims 1 to 44, which process comprises cleaving a compound according to any of claims 1 to 44 which is bound to a solid support from said solid support with an acid.

46. Compounds according to any of claims 1 to 44, when manufactured by a process according to claim 45.

47. Pharmaceutical composition comprising a compound according to any of claims 1 to 44 and a pharmaceutically acceptable carrier and/or adjuvant.

48. Compounds according to any of claims 1 to 44 for use as therapeutic active substances, particularly as therapeutic active substances for the treatment and/or prophylaxis of diseases which are associated with melanocortin-4-receptor such as obesity.

49. A method for the treatment and/or prophylaxis of diseases which are associated with melanocortin-4-receptor such as obesity, which method comprises administering a compound according to any of claims 1 to 44 to a human being or animal.

50. The use of compounds according to any of claims 1 to 44 for the treatment and/or prophylaxis of diseases which are associated with melanocortin-4-receptor such as obesity.

51. The use of compounds according to any of claims 1 to 44 for the preparation of medicaments for the treatment and/or prophylaxis of diseases which are associated with melanocortin-4-receptor such as obesity.

52. The novel compounds, processes and methods as well as the use of such compounds substantially as described hereinbefore.